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RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP

PART I

INTRODUCTORY ARTICLE AND ARTICLES 1 TO 10

By C. S. Hudson

ABSTRACT

In 1909 a beginning was made in correlating the structures of sugars with their rotatory powers by the author's application of Van't Hoff's hypothesis of optical superposition to the sugars and various of their derivatives. This method of correlation was extended in numerous subsequent articles to the lactones, the amides and phenylhydrazides, the compound sugars and glycosides, and many other optically active substances. The method and its results and the new experimental data obtained in the course of these researches have come into extensive use in the fields of organic and stereochemistry. In the present work the author's various articles have been systematically arranged and republished, either in full or with some condensations. It is hoped that the orderly presentation of the subject will assist research workers in the use of this new method of investigation in stereochemistry.

CONTENTS

I. INTRODUCTION

In this publication there are reprinted in Section III, pages 309 to 378 the first 10 articles of a series entitled "Relations Between Rotatory Power and Structure in the Sugar Group" which were originally published in the Journal of the American Chemical Society. As an introduction to them there has been prepared a summary (Sec. II, pp. 245 to 309) of the author's earlier researches on this subject, given as far as possible in the form of quotations in order that the present publication may be used as an original source of reference. A table of the rotatory powers of those substances which have been purified and measured in the course of these investigations (Sec. IV, pp. 378 to 379) and a thorough subject and substance index (Sec. V, pp. 381 to 384) have been prepared as reference aids.

It is hoped that the orderly presentation of the work may assist research workers and advanced students of organic, physical, and biological chemistry who may be interested in carbohydrate chemistry. It is recommended to such students that they read E. F. Armstrong's "The Simple Carbohydrates and the Glucosides" or H. Pringsheim's "Zuckerchemie" before studying the present publication.

Grateful acknowledgment is made of the painstaking assistance that has been rendered by a large number of coworkers whose names will be found in connection with the description of the substances, some old and some new, which they have carefully prepared and

measured. The investigations have been carried out as projects of two Federal departments, those from the years 1909–1919 having been performed in the Bureau of Chemistry of the United States Department of Agriculture, and those subsequent to 1923 having come from the Bureau of Standards of the United States Department of Commerce.

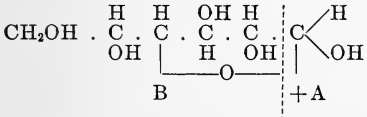
II. A SUMMARY OF THE AUTHOR'S EARLIER RESEARCHES ON RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP

This summary has been prepared in 1925 as an introduction to the 10 articles on this subject that are republished in Section III of this monograph.

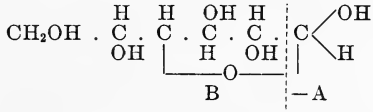
1. TWO RULES OF ROTATION IN THE SUGAR GROUP (THE ISOROTATION RULES) DERIVED FROM VAN'T HOFF'S HYPOTHESIS OF OPTICAL SUPERPOSITION

In 1909 there was proposed in an article entitled, "The significance of certain numerical relations in the sugar group," [1] a method of mathematical treatment of the dependence of rotatory power upon structure among certain carbohydrates, which consists essentially in resolving the molecular rotations of the sugars and various of their derivatives into two components and evaluating these by suitable subtractive comparisons under the assumption that the component thus eliminated has the same rotation in the two substances that are compared. In some cases this assumption is precisely the Van't Hoff hypothesis of additive optical superposition, but in many others it involves the further idea that one of the component rotations is not influenced by some changes in the molecular structure which are other than stereoisomeric. The principal argument of the 1909 article may be summarized as follows:

The weight of evidence indicates that the α and β forms of *d*-glucose have the structures (I) and (II), respectively, and the α and β forms

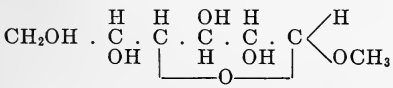


I α-*d*-Glucose, [M]=B+A

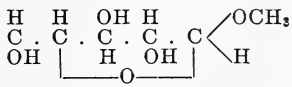


II β-*d*-Glucose, [M]=B−A

of methyl-*d*-glucoside (III) and (IV). If it be assumed that the two



III α-Methyl *d*-Glucoside



IV β-Methyl *d*-Glucoside.

[1] Hudson, Jour. Am. Chem. Soc., **31**, 66; 1909.

known modifications of glucose are the stereoisomers of the [lactonyl, see p. 272] formula, their rotatory powers should be related as follows: Let the rotation which is due to the end asymmetric carbon atom be A for one isomer, the rotation which is due to its other four asymmetric carbon atoms being B, and the molecular rotation of the whole molecule being thus $A+B$. The molecular rotation of the other isomer will then be $-A+B$, since the two isomers are identical except for the end asymmetric carbon atoms, and these are antipodes and consequently of equal but opposite rotation.[2] The sum of the molecular rotations of these isomers will accordingly be $2B$ and their difference $2A$. Now consider the molecular rotations of the similar isomers for the other sugars galactose, arabinose, lactose, mannose, etc., all of which contain the same end asymmetric carbon atom as glucose. It is true that in these sugars the carbon chain which constitutes one of the groups that is joined to the end asymmetric carbon is not always the same, but it appears from the relations which follow that for some reason its variations in the different sugars are practically without influence on the rotatory power of this carbon atom and that the latter's rotation is closely A and $-A$, respectively, for the two forms of all the aldehyde sugars and all their derivatives in which the added substance does not join directly to this end carbon atom. If the rotation of the other asymmetric carbon atoms in any one of these related sugars be called B', the molecular rotations of an α and β pair of any one of them will be $A+B'$ and $-A+B'$, and the sum of the molecular rotations will be $2B'$, which is different from the sum for the glucoses, but the difference of the molecular rotations will be $2A$, which is identical with the difference for the glucoses. It is therefore to be concluded from this theory that the difference between the molecular rotations of the α and β forms of all the aldehyde sugars and all their derivatives in which the added substance is not joined directly to the end asymmetric carbon atom is a nearly constant quantity.[3] The experimental proof of this relation is given in Table 1, from which it may be seen that though the specific rotations of the various substances vary over a wide range and the sums of the specific rotations also differ greatly there is a very satisfactory agreement of the differences of the molecular rotations, as is required by the theory.

[2] It is here assumed that the [Van 't Hoff] principle of optical superposition holds for these substances; that is, that the rotation of the remainder of the molecule is B, irrespective of whether that of the end carbon atom is A or $-A$. This principle has lately been criticised by Rosanoff (J. Am Chem. Soc., **28**, 525–533, 1906; **29**, 536–539, 1907). Although there may be some doubt as to whether the principle holds exactly, it seems to the writer that the experimental evidence on it that has been discussed by Rosanoff clearly shows that it holds closely; also, it seems quite unlikely that the simple numerical relationships that are shown in the present article, and which are based on the assumption of the correctness of the above principle, could exist if the principle did not hold at least closely. There is certainly a great need for exact experimental evidence on this principle of optical superposition, which is fundamental to the development of stereochemistry.

[3] This may be designated the first rule of isorotation. C. S. H., 1925.

TABLE 1[1]

Substance	Formula	Molecular weight	Specific rotation	Molecular rotation	Difference	Sum
α-*d*-Glucose	$C_6H_{12}O_6$	180	109	19, 600	16, 000	23, 200
β-*d*-Glucose			20	3, 600		
α-*d*-Galactose	$C_6H_{12}O_6$	180	140	25, 200	15, 700	34, 700
β-*d*-Galactose			53	9, 500		
α-*d*-Lactose	$C_{12}H_{22}O_{11}$	342	86	29, 400	17, 400	41, 400
β-*d*-Lactose			35	12, 000		

[1] In this reprinting of the original table, the data regarding arabinose have been omitted for the reason stated on p. 356.

Consider next those derivatives of glucose in which the addition or alteration affects only the end asymmetric carbon atom, the remainder of the molecule being unchanged. Such compounds are, for instance, the methyl glucosides, the structural formulas for which have already been given. The unaffected portions of the two forms of the compound will have the same rotation as these portions of the glucoses, namely B, but the end asymmetric carbon atom will now have the new rotations A' and $-A'$ in the two isomers. The molecular rotations of the two forms will thus be $A'+B$ and $-A'+B$ and their difference will be $2A'$ which is no longer equal to the difference for the glucoses, but their sum will be $2B$ and this is identical with the sum for the glucoses. It is therefore to be concluded that the two isomers of those derivatives of *d*-glucose in which only the end asymmetric carbon atom is affected will have molecular rotations whose sum is equal to the sum for the two *d*-glucoses.[4] A similar conclusion holds for the similar derivatives of the other sugars, thus the sum for the methyl galactosides must equal the sum for the galactoses, the sum for the ethyl galactosides that for the galactoses and the sum for the ethyl glucosides that for the glucoses. Lastly it may similarly be shown that the differences for the two forms of the methyl alcohol derivatives of all the aldehyde sugars is a constant quantity, and the same holds for the ethyl alcohol and other derivatives, though the constant is in each case somewhat different. * * * In Table 2 are given the data which prove the above conclusions. * * * In the last two columns letters are appended to the values of the sums and differences in order to show what values should be equal according to the foregoing theory, these equal values being indicated by the same check letter.

[4] A more general statement of this relation, which may be designated the second rule of isorotation, was given in the summary to the original article as "The α and β forms of those derivatives (for example, glycosides, etc.) of any aldose sugar in which only the end asymmetric carbon atom is affected have molecular rotations whose sum is equal to the sum for the α and β forms of the aldose."

TABLE 2

Substance	Formula	Molecular weight	Specific rotation	Molecular rotation	Difference	Sum
α-*d*-Glucose	$C_6H_{12}O_6$	180	109	19, 600	16, 000a	23, 200b
β-*d*-Glucose			20	3, 600		
α-*d*-Galactose	$C_6H_{12}O_6$	180	140	25, 200	15, 700a	34, 700c
β-*d*-Galactose			53	9, 500		
α-Methyl *d*-glucoside	$C_7H_{14}O_6$	194	157	30, 500	36, 700d	24, 300b
β-Methyl *d*-glucoside			−32	−6, 200		
α-Methyl *d*-galactoside	$C_7H_{14}O_6$	194	196	37, 900	37, 900d	37, 900c
β-Methyl *d*-galactoside			0	0		
α-Methyl *d*-xyloside	$C_6H_{12}O_5$	164	152	24, 900	35, 700d	14, 100
β-Methyl *d*-xyloside			−66	−10, 800		
α-Ethyl *d*-glucoside	$C_8H_{16}O_6$	208	151	31, 400	37, 600e	25, 200b
β-Ethyl *d*-glucoside			−30	−6, 200		
α-Ethyl *d*-galactoside	$C_8H_{16}O_6$	208	179	37, 200	38, 000e	36, 400c
β-Ethyl *d*-galactoside			−4	−800		

It seems advisable at the present time (1925) to amplify the foregoing derivation of the two rules of isorotation in order to bring out more clearly that they are deducible from the hypothesis of optical superposition in the case of some substances, but that in the general form in which they were expressed, and in which they have been shown to hold in first approximation for many substances of the sugar group, the derivation involves also a supplementary hypothesis.

The hypothesis of optical superposition, according to Patterson's [5] definition, "asserts that if in a molecule containing several asymmetric carbon atoms the part of the total rotation due to any one of these be $+A°$, then on replacing that atom by its mirror image the latter should be responsible for $-A°$ of the rotation of the new compound." In the case of substances containing three or more asymmetric carbon atoms, such as the sugars, the hypothesis asserts that the rotations of all the possible stereoisomers of a given structure are referable to rotations *A*, *B*, *C*, etc., of the asymmetric carbon atoms, the sign of each partial rotation being determined by the stereoposition of the atom concerned. The rotations of a set of stereoisomers (eight substances) containing three asymmetric carbon atoms thus become:

$$\pm R_1 = \pm A \pm B \pm C,\ \pm R_2 = \mp A \pm B \pm C,\ \pm R_3 = \pm A \mp B \pm C, \text{ and}$$
$$\pm R_4 = \pm A \pm B \mp C.$$

When the rules of isorotation were proposed (1909) it was believed that glucose and galactose were stereoisomers of the same structure—namely, (1, 4) ring aldo-hexoses. The first rule of isorotation could, therefore, be deduced for these two sugars from the hypothesis of optical superposition. But it was observed that the rule so deduced held for the rotations of the α and β forms of lactose, a sugar which differs much in structure from the hexoses. Other tests of the rules, which showed that they held in cases where their application could not be inferred from the hypothesis of optical superposition alone, were recorded. The following statement, which is

[5] Jour. Chem. Soc., **107**, 142; 1915.

a slightly altered form of the original expression already quoted (p. 246) may therefore be made. *It is true that in these sugars (glucose, galactose lactose etc.) the carbon chain which constitutes one of the groups that is joined to the end asymmetric carbon atom is not always the same structurally, but it appears from the relations that are experimentally demonstrated that its variations in the different sugars are of only small influence on the rotatory power of this carbon atom and that the latter's rotation is closely A and −A, respectively, for the α and β forms of all the aldose sugars* This statement may be termed the hypothesis of isorotation. It is an induction from experimental data and is supplementary to the hypothesis of optical superposition. There seems no likelihood *a priori* that it ever holds with mathematical exactness, but on the other hand the experimental data indicate that for many substances of the sugar group it holds closely enough to be a valuable working hypothesis in studying the relations between rotatory power and structure.

2. AN EMPIRICAL RELATION AMONG THE EQUILIBRIUM CONSTANTS OF THE MUTAROTATING SUGARS [6]

There is another numerical relation among the rotatory powers of the sugars and their derivatives which, however, seems to be only an approximate empirical relation; in any event it is not founded upon such simple theoretical premises as are the ones that have just been discussed. The α and β forms of the aldehyde and ketone sugars * * * usually establish an equilibrium in solution between the two forms and it is a fact that the ratio of the concentrations of the two forms that are in equilibrium, called the equilibrium constant, has nearly the same value for similar sugars * * *. The equilibrium constant can be calculated from the specific rotations of the pure forms and the rotation of the stable solution in which the forms are present in equilibrium. Thus, for glucose the specific rotation of the α form is 109, of the β form 20, of the stable solution 53, hence the ratio of the concentrations of the β and α forms in the stable solution is $\frac{109-53}{53-20}=1.7$

In Table 3 are given the equilibrium constants for three mutarotating sugars, from which it is seen that the constants have nearly the same values.

TABLE 3 [a]

Substance	Specific rotation		Rotation of stable solution	Equilibrium constant	Solvent
	α-form	β-form			
d-Glucose	109	20	53	1.7	Water.
d-Lactose	86	35	55	1.5	Do.
d-Galactose	140	53	86	1.6	Do.

[a] In reprinting Table 3 some glycosides and acetates, which it is now seen do not properly belong in this discussion, and arabinose (see p. 356) have been omitted from the original.

[6] Quotation from the 1909 article.

There may be added now (1925) to this subject the remark that later experimental evidence, which is obtained from Table 11, page 269, of this monograph, shows that the equilibrium coefficient $K=C_\beta/C_\alpha$, has approximately the same value for glucose ($K=1.8$), disaccharides containing glucose as their reducing constituent (for example, lactose (1.8), maltose (1.8), cellobiose (1.9), and melibiose (2.1?)), and fructose (1.7) and xylose (1.9), but that its values for many other sugars (for example, galactose (2.3), mannose (0.6), lyxose (0.7), rhamnose (0.4), arabinose (1.4), and α-glucoheptose (8.0)) are quite different. The empirical relation should, therefore, only be used cautiously.

3. A SYSTEMATIC NOMENCLATURE OF THE ALPHA AND BETA FORMS OF THE SUGARS AND THEIR DERIVATIVES[7]

Since it is clear from what precedes that a close relationship between the α and β forms extends all through the sugar group there can be little doubt that a uniform system of naming these forms by the use of these general relations will be more and more useful as the study of the sugars and their derivatives progresses. Tanret, who discovered the new forms of several of the sugars, gave them the designations α and β apparently upon the plan that the more strongly dextrorotary form should be called α. This system of naming is an arbitrary one and it can be shown that if it is followed in all cases, there will finally result the greatest confusion. Consider the following possibility. The complete antipodal stereoisomer of α-*d*-glucose must have a specific rotation equal and opposite to that for this sugar, accordingly -109, and similarly the antipode of β-*d*-glucose must have the rotation -20. Now if the preceding rule (of Tanret) is followed the form with rotation -20 must be named α-*l*-glucose since it is more dextrorotary than the other. If this be done, it results that the antipode of α-*d*-glucose will be called β-*l*-glucose and that the equilibrium constant for the *d*-glucoses will be the reciprocal for the constant of the *l*-glucoses; there will accordingly be a numerical difference between the values of a corresponding natural constant for two antipodal stereoisomers, and this conclusion seems to me an insuperable objection to such a system of naming. It may be said that the rule should be modified so that the more strongly rotating form is called α irrespective of the sign of the rotation, but such a rule would lead to even worse confusion in the case of certain sugars like rhamnose where the α and β forms have different signs of rotation and the exact numerical values are unknown.

The principles upon which a rational and systematic naming of the α and β forms may be based can be obtained from the foregoing stereochemical theory. Starting with *d*-glucose and accepting the present name for its more strongly dextrorotary form, α-*d*-glucose,

[7] Quotation from the 1909 article.

it is to be observed that the subtraction of the rotation of the β form from that of the α form gives a positive quantity, 16,200, and that the sum of the two rotations is also positive. If the naming of the *d*-glucose forms were reversed the sum of the rotations would remain a positive quantity, and this sum for the other sugars would not be identical with the value for *d*-glucose, but would vary from sugar to sugar; as the sum is not constant in quantity or sign for the related sugars and does not change sign when the names of the isomers are interchanged it is not a suitable criterion for choosing the names. On the other hand, the difference between the *d*-glucose forms is a constant, $2A = 16{,}200$, and depends only on the configuration of the end asymmetric carbon atom, which is common to all the aldehyde sugars, and changes sign to $-2A$ when the naming of the *d*-glucoses is reversed; accordingly it is as good a criterion as could be desired for naming the forms of the sugars. One point needs to be emphasized, however. If the antipodes of α-*d*-glucose and β-*d*-glucose are named α-*l*-glucose and β-*l*-glucose, and this designation seems satisfactory since it leads to identical numerical values for the equilibrium constants for the respective dextro and levo pairs of the glucoses and has already been used by Fischer[8] in naming the forms of the dextro and levo glucosides, the subtraction of the molecular rotation of β-*l*-glucose from that of α-*l*-glucose will give a negative quantity which is equal and opposite in sign to the similar difference for the *d*-glucoses. The general rule which may be proposed for naming the α and β forms of the sugars is therefore as follows: The names should be so selected that for all sugars which are genetically related to *d*-glucose[9] the subtraction of the rotation of the β form from that of the α form gives a positive difference and for all sugars which are genetically related to *l*-glucose an equal negative difference.

According to this rule, since arabinose is derived from *l*-glucose and accordingly named *l*-arabinose, though its rotation is right-handed, its unknown form with low specific rotation (see pp. 269 and 341) must be named α-*l*-arabinose, the known form of rotation 184 being β-*l*-arabinose. The difference between the molecular rotations of the two forms is then a negative quantity.

The naming of the two forms of the various derivatives of these sugars should be done with caution, as the above rule, which refers to the sugars, can not be expected to apply to the derivatives in all cases. Care should be taken to consider the rotations of the two forms of any derivative of the sugars other than glucose in connection with the rotations of the forms of the similar derivative of glucose, the naming of the forms of the glucose derivative being done by the aid of such facts as E. F. Armstrong[10] has shown, by which it is

[8] Ber., 28, 1152; 1895.

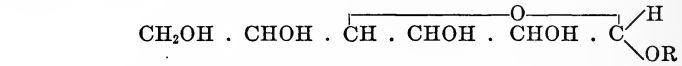
[9] A better expression for "which are genetically related to *d*-glucose" is "of the *d*-configurational series."

[10] Jour. Chem. Soc., 83, 1305; 1903.

known, for instance, that the hydrolysis of α-methylglucoside by the enzyme [α-glucosidase] liberates α-glucose, which can be distinguished from β glucose by the direction of its mutarotation. It does not seem necessary to enter into the analytical reasoning which leads to the conclusion that can be verified from Table 2 that the difference between the molecular rotations of the α and β forms of the methyl alcohol derivatives of the sugars which are genetically related to *d*-glucose (for example, the methyl *d*-galactosides) is numerically the same as the difference for the methyl alcohol derivatives of *d*-glucose and of the same sign, but that for the forms of the similar derivatives of the sugars that are genetically related to *l*-glucose the difference is again numerically equal but now of opposite sign. This conclusion leads to the following rule for naming the forms of those derivatives of the sugars in which the end asymmetric carbon atom alone is affected, such as the methyl and ethyl alcohol derivatives, the hydrazones, and many of the natural glucosides. The names of the α and β forms of the derivative of any sugar should be so selected that the difference of their rotations (α-β) is equal to and of the same sign as the difference for the two forms of the similar derivative of that glucose (*d*- or *l*-) to which the first sugar is genetically related. For those derivatives of the sugars in which the end asymmetric carbon is not affected the rule obviously reduces to that given above for the sugars themselves.

4. THE ROTATORY POWERS OF THE GLUCOSIDES

(Quotation from the 1909 article.) The numerous natural and synthetic glucosides have very similar constitutions and they may nearly all be represented, as proposed by Fischer, by the formula



where *R* denotes the group that is combined with glucose to give the glucoside and which may be, for instance, salicyl alcohol giving the glucoside salicin, coniferyl alcohol giving coniferin, or aniline giving aniline glucoside, etc. The preceding stereochemical theory shows that each of these glucosides is to be expected to exist in two modifications, the α and β forms, depending on the relative space positions of the *H* and *OR* groups that are attached to the end asymmetric carbon atom. For the methyl and ethyl glucosides and galactosides and the methyl xylosides these two forms are known but only one form of the naturally occurring glucosides is known, which in all cases seems to be the β modification, because Fischer has shown that emulsin hydrolyzes only compounds of β glucose, and α-glucosidase only compounds of α glucose, and the natural glucosides are all hydrolyzed by emulsin.[11] As the rotatory powers

[11] There are some exceptions to this statement (for example, myrosin), but the argument is not thereby changed.

of many of the natural glucosides are known, it is possible to calculate the specific rotations of the corresponding α glucosides from the previously discussed relation that the sum of the molecular rotations of a pair of α and β glucosides equals the sum for the α and β glucoses, 23,200. Of course, this relation applies only to those glucosides in which the R group is not itself optically active; this excludes amygdalin, vicianin, sambunigrin, dhurrin, and amygdonitrilglucoside, and several other cyanogenetic glucosides. If the molecular weight of the known glucoside is W and its specific rotation R_β, the specific rotation of its unknown α form is $R_\alpha = 23{,}200/W - R_\beta$. By means of this formula the specific rotations of the unknown α forms of several of the better investigated glucosides are calculated and given in Table 4.

TABLE 4.—*Calculated specific rotations of unknown α-glucosides*

Substance	Formula	Molecular weight	Specific rotation of known β form	Calculated specific rotation of α form
Salicin	$C_6H_{11}O_5.O.C_6H_4.CH_2OH$	286	−62	143
Helicin	$C_6H_{11}O_5.O.C_6H_4.COH$	284	−60	142
Arbutin	$C_6H_{11}O_5.O.C_6H_5OH$	272	−62	142
Coniferin	$C_6H_{11}O_5.O.C_{10}H_{11}O_2$	342	−67	135
Phenyl glucoside	$C_6H_{11}O_5.O.C_6H_5$	256	−71	[1] 162
Urea glucoside	$C_6H_{11}O_5.NH.CO.NH_2$	222	−24	129
Methylurea glucoside	$C_6H_{11}O_5.NH.CO.NHCH_3$	236	−30	128
Dimethylurea glucoside	$C_6H_{11}O_5.NH.CO.N(CH_3)_2$	250	−33	126
Phenylurea glucoside	$C_6H_{11}O_5.NH.CO.NHC_6H_5$	298	−55	146
Aniline glucoside	$C_6H_{11}O_5.NH.C_6H_5$	255	−52	143
Aniline lactoside [2]	$C_{12}H_{21}O_{10}.NH.C_6H_5$	417	−14	114

[1] α-Phenyl *d*-glucoside has subsequently been synthesized by Fischer and Von Michel (Ber., **49**, 2813; 1916) and its $[\alpha]_D$ found to be +180.

[2] For this compound the constant of the preceding formula becomes 41,400, which is the sum of the molecular rotations of the α and β lactoses, see Table 1, p. 247.

In these glucosides the group R, which is attached to the end carbon atom, varies considerably in composition, weight, and structure, and as it is possible to find the rotation of this end carbon atom alone the results serve to show in what manner the rotation changes with the introduction of different groups in the end carbon. It has been shown * * * that the difference of the molecular rotations of the α and β forms of any of the sugars, glucosides, etc., is twice the rotation of the end carbon atom, consequently this rotation is $(R_\alpha - R_\beta)/2$. From this formula the rotation of the end carbon atom is calculated for a number of the sugars and their derivatives as shown in Table 5. It is seen that, in general, the rotation of the end carbon atom increases with the weight of the attached group.

TABLE 5.—*Influence of different groups on the rotation of the end carbon atom of the aldose sugars*

Substance	Molecular weight	$[\alpha]_D$		Molecular rotation of end carbon	Weight of attached group
		α form	β form		
d-Glucose	180	109	20	8,000	17
d-Lactose	342	86	35	8,700	17
Methyl *d*-glucoside	194	157	−32	18,300	31
Methyl *d*-galactoside	194	196	0	18,900	31
Methyl *d*-xyloside	164	152	−66	17,800	31
Ethyl *d*-glucoside	208	151	−30	18,800	45
Ethyl *d*-galactoside	208	179	−4	19,000	45
Urea *d*-glucoside	222	[1] 129(c)	−24	17,000	59
Methylurea *d*-glucoside	236	128(c)	−30	18,000	73
Dimethylurea *d*-glucoside	250	126(c)	−33	19,900	87
Aniline *d*-glucoside	255	143(c)	−52	24,900	92
Aniline lactoside	417	114(c)	−14	26,700	92
Phenyl *d*-glucoside	256	162(c)	−71	29,800	93
Arbutin	272	147(c)	−62	28,400	109
Helicin	284	142(c)	−60	28,700	121
Salicin	286	143(c)	−62	29,300	123
Phenylurea *d*-glucoside	298	133(c)	−55	28,000	135
Coniferin	342	135(c)	−67	34,500	179

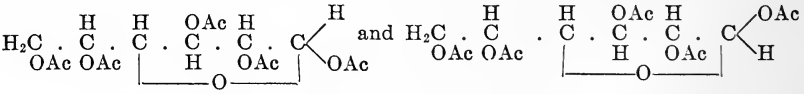
[1] The values marked (c) are calculated ones, taken from Table 4.

5. THE ROTATIONS OF ACETYL DERIVATIVES OF THE SUGARS

It was early recognized that the apparent application of the two rules of isorotation (pp. 246 and 249) to substances of the sugar group, as shown by the data of the previous Tables 1 and 2, opened the possibility of an extensive use of them in the study of the carbohydrates. It seemed desirable to test them upon the acetyl derivatives of glucose and methyl glucoside because the phenomenon of mutarotation makes the obtaining of glucose in pure α and β forms difficult, but the α and β glucose penta-acetates do not exhibit spontaneous mutarotation and can accordingly be readily purified by recrystallization. The following is quoted from an article [12] describing the results of this investigation:

(a) THE ROTATIONS OF THE GLUCOSE PENTA-ACETATES AND THE METHYL GLUCOSIDE TETRA-ACETATES

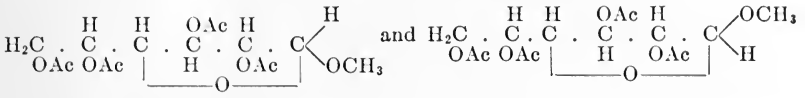
If the alpha and beta forms of glucose penta-acetate have the isomeric structures, as generally accepted,



the molecular rotations of the substances may be regarded as having the values $(A+B)$ for one form and $(-A+B)$ for the other, according to the considerations which have been presented by one of us in a

[12] Hudson and Dale, Jour. Am. Chem. Soc., **37**, 1264; 1915.

previous article.[13] The quantity A represents the rotation which is due to the end asymmetric carbon atom, and B denotes the rotation of the remainder of the structure. In similar manner, the rotations of the α and β forms of tetra-acetyl methyl glucoside,



may be written $(A'+B)$ and $(-A'+B)$, where A' is of different value from A, on account of the replacement of the acetyl by the methyl radical, but B remains of constant value. The deduction may be drawn that the sum of the molecular rotations of the two penta-acetates $(2B)$ is presumably equal to the sum of those of the two tetra-acetyl methyl glucosides $(2B)$, and this conclusion can be tested by experiment. Schliephacke [14] has calculated the data and finds that the sum is 39,700 for the penta-acetates and 54,900 for the tetra-acetyl methylglucosides, the rotations of the four substances being measured in benzene solution. The disagreement is clear, and Schliephacke concludes that the foregoing theoretical views do not apply to the acetylated derivatives of glucose. In this connection, however, it is to be noticed that one of the four substances, namely, α-tetra-acetyl methyl glucoside, has been found by Moll van Charante [15] to form a crystalline compound with benzene and to have in benzene solution a specific rotation (173°) much larger than in alcoholic solution (137°). The corresponding β form was found to have nearly identical rotations in the two solvents. It has seemed to us desirable to compare the rotations of the four substances in several solvents other than benzene since the relations seem to be complicated in the case of that solvent by the formation of a compound with one of the substances. The penta-acetates of glucose and the tetra-acetates of methyl glucoside were prepared * * * and the specific rotations of the pure substances were found to have the following values (Table 6).

[13] Jour. Am. Chem. Soc., **31**, 66; 1909 [p. 245].
[14] Ann., **377**, 182; 1910.
[15] Rec. trav. chim. Pays Bas, **21**, 42; 1902.

TABLE 6.—*Specific rotations of the glucose penta-acetates and the tetra-acetyl methylglucosides*

Solvent	Concentration	Rotation	Specific rotation $[\alpha]_D^{20}$	Molecular rotation[1] (average)	Concentration	Rotation	Specific rotation $[\alpha]_D^{20}$	Molecular rotation (average)
	g/100 cc	α-Glucose penta-acetate			g/100 cc	β-Glucose penta-acetate		
		Degrees	*Degrees*			*Degrees*	*Degrees*	
Benzene	5.302	+20.51	+ 96.7		5.061	+0.45	+2.2	
	6.313	+24.42	+ 96.7	+37,800	6.544	+0.71	+2.7	
	10.132	+39.60	+ 97.7		10.243	+1.35	+3.3	+1,100
Chloroform	5.252	+21.35	+101.6		6.303	+0.98	+3.9	
	6.738	+27.38	+101.6	+39,600	6.801	+1.04	+3.8	+1,500
	10.906	+44.36	+101.7		10.386	+1.59	+3.8	
Acetic acid (99.5 per cent)	6.325	+27.48	+108.6		6.267	+0.93	+3.7	
	10.399	+45.24	+108.8	+42,400	10.621	+1.87	+4.4	+1,600
Acetic acid (50 per cent)	3.919	+16.95	+108.1	+42,200	3.641	+0.47	+3.2	+1,200
Absolute alcohol	0.5204	+ 2.1	+100.9	+39,400	0.5411	+0.04	+1.9	+ 740
Methyl alcohol	1.4932	+ 6.25	+104.6	+40,800	1.2102	+0.24	+4.9	+1,900
	α-Tetra-acetyl methylglucoside				β-Tetra-acetyl methylglucoside			
Chloroform	4.284	+22.36	+130.5		3.813	−2.78	−18.2	
	8.178	+42.72	+130.6	+47,300	8.0396	−5.88	−18.3	−6,600
Acetic acid (99.5 per cent)	1.690	+ 9.08	+134.3		4.359	−3.40	−19.5	
	3.769	+20.16	+133.7	+48,500	8.544	−6.66	−19.5	−7,100
Acetic acid (50 per cent)	2.107	+10.60	+125.8		3.757	−3.34	−22.2	
	3.882	+19.76	+127.2	+45,800	8.002	−7.28	−22.7	−8,130
Methyl alcohol	2.138	+11.60	+135.6	+49,200	2.297	−2.00	−21.8	−7,890
Benzene[2]	4.8166	+33.84	+175.5	+63,530	4.6884	−4.28	−22.8	−8,290
Absolute alcohol[3]	1.1736	+ 6.42	+136.8	+49,500	1.48	−1.46	−24.6	−8,910

[1] The molecular weights which are used are, 390 for glucose penta-acetate and 362 for tetra-acetyl methylglucoside.

[2] Quoted from Koenigs and Knorr, *Ber.*, **34**, 970; 1901.

[3] Moll van Charante (loc. cit.) found this value to be $[\alpha]_D^{20}=+137.3°$.

The measurements refer to a temperature of 20°, sodium light, circular degrees of rotation, and the concentrations which are recorded signify the grams of substance which were contained in 100 cc of solution, the weighings having been made in air with brass weights. The tube length in all cases is 4 decimeters. The chloroform used was *chloroformum purificatum*, U. S. P.

Tanret [16] has found for the specific rotation of α-glucose penta-acetate the value +99° in benzene solution, 8 g per 100 cc, and +101.7° in chloroform, 9 g per 100 cc, and for the β form of glucose penta-acetate, he has found +2.8 in benzene, 8 g per 100 cc, and +3:7 in chloroform, 14 g per 100 cc. Our measurements confirm these values except in the case of the α form in benzene solution. Since we obtain for this substance in chloroform the same value as Tanret, it appears to us that his value in benzene must be high.

The data are now at hand for a comparison of the sums of the molecular rotations of the α and β forms of glucose penta-acetate and tetra-acetyl methylglucoside.

[16] Bull. soc. chim. [3], **13**, 261; 1895.

TABLE 7.—*Sum of the molecular rotations of the alpha and beta forms*

Substance	Chloroform	Benzene	Acetic acid		Absolute alcohol	Absolute methyl alcohol
			99.5 per cent	50 per cent		
Glucose penta-acetate	41, 100	38, 900	44, 000	43, 400	40, 100	42, 700
Tetra-acetyl methylglucoside	40, 700	55, 240	41, 400	37, 700	40, 600	41, 300

The divergence of the sums for benzene solution has already been discussed. The difference in the values in 99.5 per cent acetic acid is 2,600 in molecular rotation or approximately 7° in specific rotation, which seems larger than the uncertainty of the four measurements, and the divergence between the sums becomes greater when the proportion of water in the solvent is increased (50 per cent acetic acid). In methyl alcoholic solution the sums differ only slightly beyond the limits of experimental error. The difference in chloroform solution is only 400 in molecular rotation or about 1° in specific rotation, which constitutes good agreement with the theory. The agreement between the sums in absolute alcoholic solution is also good.

(b) THE ZINC-CHLORIDE METHOD FOR TRANSFORMING SUGAR ACETATES TO ISOMERIC FORMS

In seeking to extend such studies to the acetyl derivatives of other sugars it became necessary to devise a method for preparing certain of them which were then unknown, but the existence of which was indicated by structural theory. Thus, an octa-acetate of lactose was known, but the isomeric form that was to be expected from analogy with the two glucose penta-acetates was unknown. The origin of the method that was devised is described in the following quotation:[17]

It is now known that the two penta-acetates of glucose change easily in solution one into the other provided a suitable catalyst, such as zinc chloride, is present. Sulphuric and hydrochloric acids are also catalysts of this isomerization but sodium acetate is not. Erwig and Koenigs[18] observed that the substance which is now termed β glucose penta-acetate may be changed to the α form by heating with acetic anhydride and a trace of zinc chloride, but since they regarded the first substance as an octa-acetyl di-glucose they looked upon the change which zinc chloride brings about as one of hydrolysis rather than of isomerization, and the correct interpretation of this change was first indicated by Fischer.[19] It is important to note that Erwig and Koenigs[20] sought to change maltose

[17] Hudson, Jour. Ind. Eng. Chem., **8**, 379; 1916.
[18] Ber., **22**, 1464; 1889.
[19] Ber., **26**, 2400; 1893.
[20] Ber., **22**, 2213; 1889.

octa-acetate, which in their view was isomeric with the so-called di-glucose octa-acetate, into α glucose penta-acetate by heating it with acetic anhydride and zinc chloride, without success, and they stated that the substance remained unchanged. With present knowledge such an hydrolysis would not be expected, but on the other hand it is difficult to understand what experimental tests could have led Erwig and Koenigs to believe that the maltose octa-acetate remained unchanged, because we now know that it changes under such conditions almost completely into an isomeric octa-acetate. This point will come up again; it is here mentioned to indicate that although in fact Erwig and Koenigs were the first to change a sugar acetate to its isomer by the use of zinc chloride, they did not interpret the change correctly nor apply it further. An important study of this reaction from the physico-chemical standpoint was made by Jungius,[21] who showed that the β penta-acetate of glucose does not change completely to the α form in acetic anhydride solution containing zinc chloride, but that a balanced reaction between the two substances exists and that when equilibrium is attained 90 per cent of the α and 10 per cent of the β form are present. The quantitative measurements of Jungius show why the α form crystallizes readily from the transformed β modification, and a consideration of his results led me sometime ago to inquire whether other sugar acetates could be rearranged similarly to give an equilibrium mixture in which a new isomer might so predominate that its crystallization could be accomplished. The first experiments were made by Doctor Johnson and myself on lactose, but we considered it desirable to start with the pure octa-acetate of lactose rather than with the sugar itself in order to avoid the presence of by-products that may be produced during the acetylation. It was found that the specific rotation of a freshly prepared cold solution of the lactose octa-acetate of Herzfeld in acetic anhydride containing a trace of zinc chloride was $+4°$ and that on heating, this value rapidly changed, becoming constant at $+52°$. From the transformed solution a new crystalline octa-acetate of lactose was separated. Its specific rotation in acetic anhydride was found to be $+64$, which indicates that about 81 per cent of the new isomer was present in the equilibrium mixture from which it was crystallized. In similar manner we found that the heating of a solution of maltose octa-acetate in acetic anhydride containing zinc chloride changed its specific rotation from $+60$ to $+110°$ and from the transformed solution a new octa-acetate was crystallized.

By the use of this reaction there were soon isolated for the first time in pure crystalline form the predicted α octa-acetates of lactose, maltose and gentiobiose, the α penta-acetates of chon-

[21] Z. physik. Chem., 52, 101; 1905.

drosamine, mannose and galactose (second penta-acetyl galactose), the α tetra-acetate of xylose and the β tetra-acetate of arabinose. In the course of this work nearly all the previously known crystalline fully-acetylated derivatives of the sugars were re-prepared, carefully purified, and their rotations in chloroform were measured. The following quotations summarize the main results:

It [22] has been shown in previous articles [23] that considerations of molecular structure lead to the conclusion that the differences in molecular rotations between the α- and β-forms of the fully acetylated aldose sugars should be equal. The experimental evidence in support of this relationship is collected in the accompanying table which includes the molecular rotations in chloroform at 20° of all the previously described pairs of completely acetylated aldose sugars.

TABLE 8

Substance	Molecular rotation of α-form	Molecular rotation of β-form	Difference
d-Glucose penta-acetate	+39, 600	+1, 500	+38, 100
Lactose octa-acetate	+36, 500	−2, 900	+39, 400
Maltose octa-acetate	+83, 050	+42, 500	+40, 500
Cellobiose octa-acetate	+27, 800	−10, 200	+38, 000
d-Glucosamine penta-acetate	+36, 400	+470	+35, 930
d-Chondrosamine penta-acetate [1]	+39, 500	+4, 100	+35, 400
Gentiobiose octa-acetate	+35, 500	−3, 600	+39, 100
d-α-Glucoheptose hexa-acetate	+40, 200	+2, 200	+38, 000
d-Mannose penta-acetate	+21, 400	−9, 800	+31, 200
d-Galactose penta-acetates (1 and 2)	+41, 600	+8, 900	+32, 700
d-Galactose penta-acetates (3 and 4)	+23, 800	−16, 400	+40, 200
d-Xylose tetra-acetate	+28, 300	−7, 900	+36, 200
l-Arabinose tetra-acetate	+13, 400	+46, 800	[2] −33, 400

[1] Since Levene (J. Biol. Chem., **31**, 609; 1917) has shown that chondrosamine belongs in the *d*-series of sugars, he having synthesized it from *d*-lyxose, the naming of its α- and β-penta-acetates must be changed from that which we used in a former article (Jour. Am. Chem. Soc., **38**, 1431; 1916) and the more levorotatory form designated as β.

[2] The negative sign of this value follows from the system of nomenclature of α- and β- forms because the sugar belongs to the *l*-series. The difference for *d*-arabinose tetra-acetates would be +33,400, conforming in sign to the values for the other *d*-sugars of the table.

Since [24] the nonreducing sugars [for example, sucrose, trehalose, etc.] do not occur in α and β forms, only one fully acetylated derivative is to be expected for each of them, and only one is known. The rotatory powers of sucrose and trehalose octa-acetates in acetic anhydride solution are not affected by heating in the presence of zinc chloride, showing that there is no transformation to isomers.[25]

[22] Quotation from J. Amer. Chem. Soc., 40, 993 (1918). The third and fourth galactose penta-acetates have been added to the table of the original article.

[23] Jour. Amer. Chem. Soc., **37**, 1270, 1276, 1280, 2748; 1915; **38**, 1431, 1575; 1916; **39**, 1272; 1917; J. Ind. Eng. Chem., 8, 379; 1916.

[24] Quoted from Jour. Ind. Eng. Chem., **8**, 379; 1916.

[25] Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 2752; 1915.

It is only recently that the behavior of any acetate of a ketose sugar toward isomerization has been investigated. Starting with a crystalline tetra-acetate of fructose which Doctor Brauns discovered some years ago, we [26] have prepared from it two crystalline isomeric penta-acetates of fructose which appear to constitute an α and β pair. Neither of these penta-acetates changes, however, to the other form when heated with acetic anhydride and zinc chloride and it may be, therefore, that the establishment of an equilibrium between α and β acetates is limited to the derivatives of the aldose sugars.

(c) NEW RING FORMS OF SUGAR DERIVATIVES. THE FOUR ISOMERIC PENTA-ACETATES OF GALACTOSE

Steps in the advancement of chemical theory have often occurred as the result of the discovery of more isomers than could be accounted for by accepted principles. Thus, the discovery of two penta-acetates of glucose, two methyl glucosides and two forms of glucose caused the acceptance of the Tollens γ-cyclo structure for the sugar in place of the older aldehyde formula. A similar overgrowing of the bounds of the past is now in progress, having had its start in the discovery of a third form of methyl glucoside by Fischer.[27] The substance is amorphous and probably consists of a mixture of isomers, and its difference from the two known methyl glucosides lies in the fact that it is distillable. Fischer considers that its existence is to be accounted for on the ground that the ring is formed on some other than the γ-carbon atom. Recently while studying the acetylation of galactose with acetic anhydride and sodium acetate, I noticed the crystallization of a substance which proved to be a third penta-acetate of galactose.[28] By the treatment of this third substance with acetic anhydride and zinc chloride it has been rearranged [29] to a fourth crystalline penta-acetate of galactose. The first and second isomers establish an equilibrium in the rearranging solution,[30] and the third and fourth forms do likewise, but it has not been possible to rearrange a member of the one pair into a member of the other. This fact leads to the view that the four penta-acetates consist of the α and β forms of two pairs and that the pairs differ in structure by the position of the internal ring.

The melting points and specific rotations in chloroform of these four crystalline isomeric penta-acetates of galactose are:

First galactose penta-acetate, m. p. 142°, $[\alpha]_D = +23$; second galactose penta-acetate, m. p. 96°, $[\alpha]_D = +107$; third galactose penta-acetate, m. p. 98°, $[\alpha]_D = -42$; fourth galactose penta-acetate, m. p. 87°, $[\alpha]_D = +61$.

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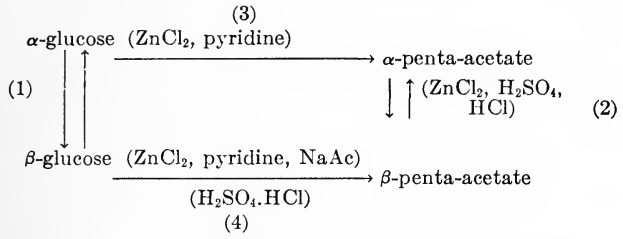
[26] Hudson and Brauns, Jour. Am. Chem. Soc., **37**, 1283, 2736; 1915.
[27] Ber., **47**, 1980; 1914.
[28] Jour. Am. Chem. Soc., **37**, 1591; 1915.
[29] Hudson and Johnson, Jour. Am. Chem. Soc., **38**, 1223; 1916.
[30] Hudson and Parker, Jour. Am. Chem. Soc., **37**, 1589; 1915.

(*d*) A CORRELATION OF THE REACTIONS FOR ACETYLATING SUGARS[31]

It is possible at the present time to summarize fairly well the numerous reactions which have been observed in the acetylation of the sugars. For this purpose the sugar group may be divided into three classes, the nonreducing sugars, such as sucrose and trehalose, the aldoses, and the ketoses:

I. The acetylation of the nonreducing sugars gives only one fully acetylated derivative independent of the catalyst used.

II. Selecting glucose as an illustration of the aldose class for the reason that its reactions have been thoroughly studied, the known steps in the acetylation of an aldose sugar may be indicated in the diagram as four reactions, two of which are reversible and two irre-



versible. The acetylation of either α- or β-glucose with acetic anhydride and sodium acetate requires warm temperature and as a result the isomerization of the sugar [reaction (1)] precedes its acetylation and the β-penta-acetate is produced because β-glucose (and the other β-aldoses) acetylate (4) more readily than the α-form. It is evident why the final product by this method of acetylation consists largely of the β-penta-acetate, no matter whether α- or β-glucose is used at the start. When zinc chloride is used as the catalytic agent, two cases have to be considered, depending upon whether the temperature is kept low (0°) or high. If it is low, reactions (1) and (2) are very slow and reactions (3) or (4) can be produced without the occurrence of isomerization. Starting with the pure form of either α- or β-glucose, the correlated penta-acetate can be produced in this way. At low temperatures the same correlation results from the acetylation with acetic anhydride and pyridine. On the other hand, if the temperature is warm, reaction (2) proceeds rapidly when $ZnCl_2$ or H_2SO_4 or HCl is the catalyst and as a result the equilibrium mixture of α- and β-penta-acetate is obtained no matter which form of the sugar is acetylated; and since this equilibrium is far toward the α-acetate in the case of glucose and all other aldoses which have been tested, the α-penta-acetate is the substance which forms the crystalline product of the reaction.

[31] Quoted from Jour. Ind. Eng. Chem., 8, 379; 1916.

III. The acetylation of the ketoses is only vaguely understood at present and only one representative of the class (fructose) has been investigated. It appears that reaction (2), the isomerization of the penta-acetates, does not take place and the whole scheme is thereby made different. Further investigations will be required before the acetylation of the ketoses is fully understood.

The fully acetylated derivatives of the sugars are the most accessible materials for the preparation of many important sugar derivatives—thus glucose penta-acetate yields bromo-acetyl glucose and from it many synthetic glucosides, as well as glucose tetra-acetate, may be obtained—and it is reasonable to suppose that the present knowledge of the mechanism of the acetylation reaction will permit in the future its control and efficient utilization in the production of new substances.

(e) THE ROTATIONS OF THE ACETATES OF THE ALPHA AND BETA FORMS OF METHYL XYLOSIDE, GLUCOSIDE, AND GALACTOSIDE [32]

A comparison can also be made between the two tri-acetyl-methyl-xylosides, the corresponding two tetra-acetyl-methyl-glucosides and the tetra-acetyl-methyl-galactosides. If $(A+B)$ represents the molecular rotation of α-tri-acetyl-methyl-xyloside where A is the rotation of the end asymmetric carbon atom and B that of the remainder of the molecule, the molecular rotation of β-tri-acetyl-methyl-xyloside may be represented by $(-A+B)$. In similar manner let $(A+B')$ and $(-A+B')$ represent the molecular rotations of the α- and β-tetra-acetyl-methyl-glucosides and $(A+B'')$ and $(-A+B'')$ those of the α- and β-tetra-acetyl-methyl-galactosides. The difference between the rotations of each of these pairs is the same quantity, $2A$. This conclusion is tested in Table 9, the rotations referring to chloroform (U. S. P.) solutions.

TABLE 9

Compound	Molecular weight	$[\alpha]_D^{20}$	Molecular rotation	One-half difference of molecular rotation for each pair (A)	One-half sum (B)
α-Tri-acetyl-methyl-*d*-xyloside	290	+119.6	+34,700	+26,150	+8,550
β-Tri-acetyl-methyl-*d*-xyloside	290	−60.7	−17,600		
α-Tetra-acetyl-methyl-*d*-glucoside	362	+130.5	+47,300	+26,950	+20,350
β-Tetra-acetyl-methyl-*d*-glucoside	362	−18.3	−6,600		
α-Tetra-acetyl-methyl-*d*-galactoside	362	+133.0	+48,400	+26,550	+21,850
β-Tetra-acetyl-methyl-*d*-galactoside	362	−13.0	−4,700		

The agreement of the values of A is satisfactory.

[32] Quoted from Hudson and Dale, Jour. Am. Chem. Soc., **40**, 997; 1918.

(f) OPTICAL SUPERPOSITION AMONG THE ACETYLATED DERIVATIVES OF XYLOSE [33]

From a comparison of the molecular structures of the α- and β-penta-acetates of glucose and the α- and β-tetra-acetyl-methyl-glucosides the conclusion was drawn that the sum of the molecular rotations of the two penta-acetates is presumably equal to the sum of the molecular rotations of the two tetra-acetyl-methyl-glucosides, and this deduction was well verified by measurements of the specific rotations of the four compounds. A similar relation exists between the molecular structures of the α- and β-tetra-acetates of xylose and the α- and β-tri-acetyl-methyl-xylosides, hence, it is to be expected that the sum of the molecular rotations of the α- and β-tetra-acetates of xylose is equal to that of the α- and β-tri-acetyl-methyl-xylosides.

In Table 10 are recorded the specific and molecular rotations of these compounds in chloroform (U. S. P.) solution, while in the last column the sums of the molecular rotations of the two pairs are shown.

TABLE 10

Compound	Molecular weight	$[\alpha]_D^{20}$	Molecular rotation	One-half sum of molecular rotation of each pair
α-Xylose tetra-acetate	318	+89.1	+28,300	+10,200
β-Xylose tetra-acetate	318	−24.9	−7,900	
α-Tri-acetyl-methyl-xyloside	290	+119.6	+34,700	+8,550
β-Tri-acetyl-methyl-xyloside	290	−60.7	−17,600	

The agreement is not so good as it was in the case of the similar derivatives of glucose.

(g) THE ROTATIONS OF THE BETA HEPTA-ACETATES OF METHYL MALTOSIDE AND METHYL CELLOBIOSIDE [34]

If the molecular rotations of the α and β forms of tetra-acetyl methyl glucoside are denoted by $(A+B)$ and $(-A+B)$,[35] respectively, the molecular rotations of the α and β forms of hepta-acetyl methyl maltoside may be expressed as $(A+B')$ and $(-A+B')$, respectively, where A represents the rotation that is due to the terminal asymmetric carbon atom and B or B' that due to the remainder of the corresponding structures. The difference of the rotations of the α and β forms of the acetylated glucosides is $2A$, and it has been shown in the article cited that this value is +53,900, hence $A = +26{,}950$. If the value of B' were known it should be possible, knowing A, to calculate the rotations of the two forms of hepta-acetyl methyl maltoside. A value for B' can be obtained

[33] Quotation from Hudson and Dale, Jour. Am. Chem. Soc., **40**, 998; 1918.
[34] Quoted from Hudson and Sayre, Jour. Am. Chem. Soc., **38**, 1867; 1916.
[35] Hudson and Dale, Jour. Am. Chem. Soc., **37**, 1264; 1915.

from the observed molecular rotations of the α and β forms of maltose octa-acetate, since this substance differs in structure from acetylated methyl maltoside only in respect to the terminal asymmetric carbon atom, which has the acetyl group in place of the methyl. The rotations of the two forms of the octa-acetate may accordingly be expressed as $(A'+B')$ and $(-A'+B')$ and their sum is $2B'$, which has been found to be $+125{,}400$,[36] or $B'=+62{,}700$. Hence the specific rotation of α hepta-acetyl methyl maltoside (M. W. 650) is calculated to be $(+26{,}950+62{,}700)/650=+138°$, and that of the β modification $(-26{,}950+62{,}700)/650=+55°$. Fischer and Armstrong [37] have prepared from the action of silver carbonate upon aceto-chloro-maltose in methyl alcoholic solution a crystalline hepta-acetyl methyl maltoside, of m. p. 121–122°, but they have not recorded its rotation. By the same method Foerg [38] prepared the same substance, found it to melt at 125–127°, but did not record its rotation. Koenigs and Knorr [39] prepared from aceto-nitro-maltose in methyl alcoholic solution by the action of barium carbonate and a trace of pyridine, a hepta-acetyl methyl maltoside of m. p. 128–129° and specific rotation in benzene +61°. Judging from the values of the melting points, the substances are identical and probably consist of the β form, because the aceto-halogeno sugar derivatives yield, in general, the glucosides of that series. The nearness of the recorded rotation in benzene (+61°) to that calculated for the β modification in chloroform (+55°) also supports this conclusion, but we have considered it necessary to prepare the substance anew in order that its rotation in chloroform might be measured. The value which we find in this solvent is +54°, which agrees almost exactly with the calculated rotation and proves clearly that the substance is the β form of hepta-acetyl methyl maltoside. While no method is known for preparing the α modification, the agreement between calculation and experiment in the case of the β form makes it very probable that the calculated value for the α form is not far from correct.

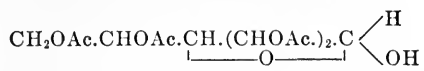
By precisely similar calculation the rotations of the α and β forms of hepta-acetyl methyl cellobioside may be calculated, the rotation of the acetylated cellobiose chain B'' being obtained from the rotations of the α and β forms of cellobiose octa-acetate. It has been found that $B''=+8{,}800$,[40] hence the specific rotation of α hepta-acetyl methyl cellobioside (M. W. 650) is written $(+26{,}950+8{,}800)/650=+56°$ and that of the β form $(-26{,}950+8{,}800)/650=-28°$. Skraup and Koenigs [41] have prepared from aceto-chloro-cellobiose in methyl alcoholic solution by the action of silver carbonate a hepta-acetyl

[36] Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 1277; 1915.
[37] Ber., **34**, 2895; 1901.
[38] Monatsh., **23**, 48; 1902.
[39] Ber., **34**, 4344; 1901.
[40] Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 1278; 1915.
[41] Monatsh., **22**, 1034; 1901.

methyl cellobioside which melted at 173°, but its rotation is not recorded. We have prepared this substance in pure condition and find it to melt at 187° (uncorr.) and to show the specific rotation in chloroform of $-25.4°$, which is in good agreement with the calculated value for β-hepta-acetyl methyl cellobioside.

(h) THE ROTATIONS OF THE BETA HEPTA-ACETATES OF MALTOSE, CELLOBIOSE AND LACTOSE [42]

If the α and β forms of glucose tetra-acetate



were known, it should be possible to obtain from the difference of their molecular rotations the value of the rotatory power of the end asymmetric carbon atom, and by combining this value with those for the acetylated maltose, cellobiose or lactose chains, to obtain the rotations of the respective hepta-acetates of these biose sugars. These calculations would be entirely similar in method to those just indicated. Since the α form of glucose tetra-acetate has not been described, it is necessary to base the calculations upon some other similar pair of derivatives, and we have selected the α [43] and β [44] tetra-acetates of galactose, which have recently been carefully purified in this laboratory, and their rotations in chloroform found to be $+141°$ and $+22°$.[45] If the rotation of their end asymmetric carbon atom be written A'' and that of the acetylated galactose residue $B''\,'$, the molecular rotation (M. W. 348) for the α form is $(A''+B''\,')$, for the β $(-A''+B''\,')$, and the difference is $2A''$, $(141-22)348 = +41{,}400$, hence $A''=20{,}700$. Using this value, the specific rotation of α maltose hepta-acetate (M. W. 636) is calculated to be $(+20{,}700+62{,}700)/636=+131°$, while that of the β modification becomes $(-20{,}700+62{,}700)/636=+66°$. E. and H. Fischer [46] prepared the β form from aceto-chloro-maltose and record its melting point as 179–180° (corr.) and its initial specific rotation in acetylene tetrachloride $+72.6°$, rising slowly to 76.7°. The rise is probably due to the slow establishment in solution of equilibrium between the α and β forms by the mutarotation reaction. We have prepared and purified this β form in order to measure its rotation in chloroform. The initial product showed $[\alpha]_D=+78°$ in this solvent, but on successive recrystallizations of the material from chloroform and ether, the value slowly fell; and only after 16 recrystallizations did it become constant, indicating that the material was the pure β form. The

[42] Quotation from Hudson and Sayre, Jour. Am. Chem. Soc., **38**, 1867; 1916.
[43] Skraup and Kremann, Monatsh., **22**, 1045; 1901.
[44] Unna, Inaugural Diss., Berlin, 1911, p. 2.
[45] Hudson and Yanovsky, new measurements. See Jour. Am. Chem. Soc., **38**, 1226–1227; 1916.
[46] Ber., **43**, 2523; 1910.

specific rotation of the pure substance was $+67.8°$ in chloroform, which agrees well with the calculated value for β-maltose hepta-acetate.

The specific rotations of the α and β hepta-acetates of cellobiose may be calculated in the same manner from the data already mentioned, to be $(+20{,}700+8{,}800)/636=+46°$ for the α and $(-20{,}700+8{,}800)/636=-19°$ for the β modification. The cellobiose hepta-acetate which Fischer and Zemplén[47] prepared from iodo-acetyl cellobiose melted at 195–197° and showed $[\alpha]_D=20°$ in chloroform. We have prepared this substance from aceto-bromo-cellobiose and obtained $+18°$ for the rotation of the crude substance; but on recrystallization the value gradually became lower without, however, becoming constant before the supply of material was exhausted. After 18 recrystallizations the value was $-2°$, which is 17° from the calculated value, but it seems reasonable to suppose that further purification would bring the values nearer.

The specific rotations of the α and β forms of lactose hepta-acetate may be calculated from $A''=+20{,}700$ and $B''\,''=+16{,}600$, which is the value for one-half the sum of the molecular rotations of the α and β octa-acetates of lactose,[48] to be $(+20{,}700+16{,}600)/636=+59°$ for the α, and $(-20{,}700+16{,}600)/636=-6°$ for the β form. We have prepared lactose hepta-acetate, which does not appear to have been crystallized previously, by the action of silver carbonate on aceto-bromo-lactose in acetone solution. As in the case of cellobiose hepta-acetate, the amount of material available was not sufficient for completely purifying the β form. The crude product, rotating $+12°$ in chloroform, was recrystallized 20 times, yielding a substance of rotation $-0.3°$ in chloroform, which is about 6° higher than that calculated for β-lactose hepta-acetate. Since the rotation has not yet reached a constant value, it is to be supposed that further purification would have made the agreement closer.

(i) THE ROTATIONS OF THE ALPHA AND BETA METHYL GENTIOBIOSIDES AND THEIR HEPTA-ACETATES[49]

In a previous article[50] it was shown that the rotatory powers of the α- and β-forms of gentiobiose can be calculated from the rotations of sucrose, gentianose and the α- and β-forms of *d*-glucose. The values thus obtained were $+39$ and -11 for α- and β-gentiobiose, respectively. Let us now calculate the rotatory powers of the corresponding α- and β-methyl gentiobiosides by the method which has previously been explained in connection with the rotations of the methyl glucosides.[51] The molecular rotation of methyl gentiobioside is assumed to be the sum of the rotation of the gentiobiose chain (*Gb*) and the rotation of the asymmetric lactonyl carbon atom (*B'*)

[47] Ber., **43**, 2539; 1910.
[48] Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 1270; 1915.
[49] Quoted from Hudson and Johnson, Jour. Am. Chem. Soc., **39**, 1272; 1917.
[50] Hudson, Jour. Am. Chem. Soc., **38**, 1569; 1916. (See p. 275.)
[51] Hudson, Jour. Am. Chem. Soc., **31**, 66; 1909.

of the methyl glucosides. The molecular rotation of the gentiobiose (m. w. 342) chain (*Gb*) is $(39-11)342/2=4{,}790$, and the value of *B'* has been shown to be 18,430.[52] Since the molecular weight of methyl gentiobioside is 356, the specific rotation in water of its α-modification is calculated to be $(Gb+B')/356=+65°$ and that of its β-form to be $(Gb-B')/356=-38°$.

In quite similar manner the rotations of the hepta-acetyl methyl gentiobiosides may be calculated.[53] The molecular rotation of the acetylated gentiobiose chain (*Gb'*) may be obtained from the previously mentioned specific rotations in chloroform of the α- and β-octa-acetates of gentiobiose (m. w. 678), to be $(52-5)678/2=15{,}900$. The value of the rotation of the lactonyl carbon of the acetylated methyl glucosides (*B''*) has been found[54] to be 26,900, hence the specific rotation of hepta-acetyl α-methyl gentiobioside (m. w. 650) in chloroform is calculated to be $(Gb'+B'')/650=+66°$ and that of the β-form to be $(Gb'-B'')/650=-17°$.

Starting with the known β-octa-acetate of gentiobiose, it was converted to bromo-acetyl gentiobiose, which was obtained as a sirup, and from this were produced in order crystalline β-hepta-acetyl methyl gentiobioside and β-methyl gentiobioside. The rotations of these pure substances were found to agree closely with the calculated values. (See also p. 374.)

Substance	Solvent	Observed $[\alpha]_D^{20}$	Calculated $[\alpha]_D^{20}$
β-Hepta-acetyl methyl gentiobioside	Chloroform	−19	−17
β-Methyl gentiobioside	Water	−36	−38

6. INDIRECT MEASUREMENTS OF THE ROTATORY POWERS OF SOME ALPHA AND BETA FORMS OF THE SUGARS BY MEANS OF SOLUBILITY EXPERIMENTS[55]

At the present time the crystalline α and β modifications of lactose and of glucose are known in a condition closely approaching purity and their rotatory powers have in consequence been directly measured. The view that the mutarotation of lactose and glucose is due to the slow establishment of an equilibrium in solution between the respective α and β forms of these sugars leads to the presumption that the many other sugars which show mutarotation exist in α and β forms likewise. Such modifications have, indeed, been crystallized in the case of galactose, rhamnose, gentiobiose and possibly melibiose, but it appears doubtful whether the isomers have been fully sepa-

[52] Jour. Am. Chem. Soc., **31** [illegible]: 1909 In the present calculation the more recent values of Bourquelot (J. pharm. chim., [7] **14**, 2; 1916) are used namely $[\alpha]_D^{20}$ for α-methyl glucoside=+157.9° and for the β-isomer=−32.5°.

[53] Hudson and Sayre, Jour. Am. Chem. Soc., **38**, 1867; 1916.

[54] Hudson and Dale, Jour. Am. Chem. Soc., **37**, 1265; 1915.

[55] Quoted from Hudson and Yanovsky, Jour. Am. Chem. Soc., **39**, 1013; 1917.

rated in these cases. For the remaining crystalline sugars which show mutarotation and, therefore, probably exist in two modifications, namely, xylose, arabinose, lyxose, ribose, mannose, fructose, α-glucoheptose, maltose, cellobiose, and a few rarer sugars, only one crystalline form has ever been prepared.

It has been suggested by one of us [56] that the difference between the molecular rotations of the α and β forms of the sugars is a constant quantity, or nearly so, for all the aldoses, and by use of this relationship the rotatory powers of several of the unknown forms have been calculated from those of the known modifications. Thus, since the specific rotations of α and β lactose are 90 and 35°, respectively, and that of β maltose (so named because it shows upward mutarotation) is 118°, the rotation of the unknown α maltose is calculated to be $118+(90-35)=173°$. In the present investigation we have sought to obtain experimental evidence regarding the rotations of these unknown forms of the mutarotating sugars. The principle which has been used is that the rotation of the unknown form may be measured either by observing the maximum rate of solution of the corresponding known isomer or by measuring the latter's initial and final solubility, a method which has previously been described and applied in the case of the α and β forms of lactose.[57]

(a) DESCRIPTION OF THE METHOD

The theory of the maximum rate of solution of any mutarotating sugar may be taken from the considerations that were presented regarding lactose in the former article. Thus, if an excess of pure crystalline α glucose is shaken continuously at constant temperature with a solvent in which it is only slightly soluble, so that the laws of dilute solutions apply, the initial solubility (S_o), the final solubility (S_∞), and the solubility (S) at any time (t) since the beginning of the experiment, are connected by the relation $1/t \log [(S_\infty - S_o)/(S - S_o)] = k_2$, where k_2 is the velocity-coefficient expressing the rate at which unit concentration of dissolved β glucose changes to the α form. The analogous coefficient for the reverse change of α to β is k_1, and the value of the sum of these coefficients (k_1+k_2) may be obtained independently from measurements of the rate of mutarotation of either form of the sugar, as has previously been shown. It was also there proved that the equilibrium-constant (K) for the reversible reaction is equal to k_1/k_2, and also to $(S_\infty - S_o)/S_o$. It is evident that the ratio (K) of the amounts of the β and α forms that are present when equilibrium is attained may be found either by determining k_1 and k_2 from combined measurements of the rate of mutarotation (k_1+k_2) and the maximum rate of solution of the known form (k_2), or by observing the initial and final solubilities of

[56] Hudson, Jour. Am. Chem. Soc., **31**, 66; 1909.

[57] Hudson, Z. physik. Chem., **44**, 487; 1903; Jour. Am. Chem. Soc., **26**, 1067; 1904. *See also* Lowry, Jour. Chem. Soc., **85**, 1551; 1904

this substance. With this ratio determined and the specific rotations of α glucose and the equilibrium mixture known, it is possible to calculate the rotatory power of the β form. Since the solubilities are more easily and accurately observed than the rates of mutarotation and solution, we have usually chosen to measure only them, though in the case of two sugars (mannose and fructose) the values of K have been determined by both methods with agreeing results.

(*b*) EXPERIMENTAL RESULTS

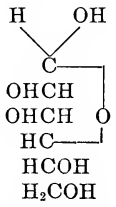
The experimental results that were obtained in this study were summarized as follows:

It is generally recognized that the sugars which show mutarotation (for example, the aldoses and ketoses) differ from those which do not by the following characteristics: (1) Existence in α and β forms, though one of these forms may not have been isolated in the crystalline state; (2) power of combining with phenylhydrazine; and (3) of reducing Fehling's solution. It is now shown that the mutarotating sugars have another common property, namely, a measurable maximum rate of solution which is caused by the slow establishment in solution of the equilibrium between the α and β forms of the sugar. The nonreducing, nonmutarotating sugars (for example, sucrose, trehalose, raffinose) do not show this maximum rate of solution. By measuring the maximum rate of solution, or the initial and final solubilities, of many of the mutarotating sugars, it has been possible to obtain experimental evidence on the rotatory powers of those forms of these sugars which have as yet not been crystallized and measured directly. In the following table a summary is recorded of the specific rotations, in water at 20°, of the α and β forms of nearly all the sugars which show mutarotation, together with the final specific rotations that refer to the equilibrium mixture of the α and β forms. The values that are printed in italics have been obtained by the indirect measurements of the initial and final solubilities, as described in this article, and the other values are the result of direct observation.

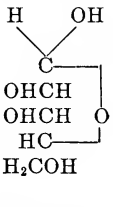
TABLE 11.—*Rotatory powers of the mutarotating sugars*

Sugar	M. w.	Formula	Specific rotation in water $[\alpha]_D$			Molecular rotation difference
			α form	Constant rotation	β form	
d-Glucose	180	$C_6H_{12}O_6$	+113.4	+52.2	+19	+16,900
d-Galactose	180	$C_6H_{12}O_6$	+144.0	+80.5	+52	+16,600
d-Mannose	180	$C_6H_{12}O_6$	*+34*	+14.6	−17	+9,180
d-Fructose	180	$C_6H_{12}O_6$	*−21*	−92.0	−133.5	
d-Xylose	150	$C_5H_{10}O_5$	+92	+19	*−20*	+16,800
d-Lyxose	150	$C_5H_{10}O_5$	+5.5	−14	*−36*	+6,220
d-Arabinose	150	$C_5H_{10}O_5$	*−54*	−105	−175	+18,100
l-Rhamnose	164	$C_6H_{12}O_5$	−7.7	+8.9	*+54*	−10,000
α-Glucoheptose	210	$C_7H_{14}O_7$	*+45*	−20.4	−28.4	+15,300
Lactose	342	$C_{12}H_{22}O_{11}$	+90.0	+55.3	+35	+18,800
Maltose	342	$C_{12}H_{22}O_{11}$	*+168*	+136	+118	+17,100
Melibiose	342	$C_{12}H_{22}O_{11}$	*+179*	+142.5	+124	+18,800
Cellobiose	342	$C_{12}H_{22}O_{11}$	*+72*	+35	+16	+19,200

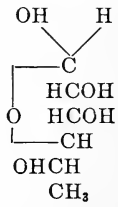
In the last column are recorded the differences between the molecular rotations of the respective α and β forms of each aldose. If the rotatory power of the end asymmetric carbon atom in these aldoses has the value $+A$ for the α-sugar and $-A$ for the β form, and the rotation of the remainder of the structure is B, the molecular rotation of an α-sugar is $A+B$, and of its β form $-A+B$, and the difference of these values is $2A$. It is to be expected, on the view that the value of A is not influenced by changes in the configuration of the remainder of the molecule, that this difference $2A$ is a constant for all the aldoses. The last column shows that the theory is fairly well borne out except in the case of mannose, lyxose, and rhamnose. Fructose is not considered since it is a ketose and does not apply in the theory. The negative sign for the difference in the case of rhamnose is the result of the system of nomenclature for the α and β forms and is due to the fact that rhamnose is an *l*-series sugar. Now the configurations of *d*-mannose, *d*-lyxose and *l*-rhamnose are



d-Mannose.



d-Lyxose.



l-Rhamnose.

and it will be observed that these configurations are identical (or antipodal) from the γ-carbon atom upward. It appears probable, therefore, that the exceptional value of the difference for these sugars may be dependent upon this type of configuration. Since, however, α-glucoheptose has the same configuration from the γ-carbon upward, and nevertheless shows a molecular difference nearer, though not equal, to the average value for most of the aldoses, this possible connection between structure and exceptional rotation remains in some doubt. In the case of closely related sugars, such as the four disaccharides, the agreement of theory and experiment is very good when it is recalled that it has been possible to make the measurements only by an indirect procedure.

The speeds of mutarotation of most of the sugars are indicated in the following table, the values for lyxose, α-glucoheptose, melibiose, and cellobiose being recorded for the first time:

TABLE 12.—*The velocity-coefficients of the mutarotation of the sugars in water at 20°*

Sugar	$k_1+k_2=\frac{1}{t}\log\frac{r_0-r\infty}{r-r\infty}$ (minutes and decimal logarithms)
Fructose	[1] 0.082
Lyxose	[2] .065
Rhamnose	[2] .039
Arabinose	[3] .031
Fucose	[4] .022
Xylose	[3] .021
Mannose	[5] .0190
α-Glucoheptose	.0122
Galactose	[3] .0102
Melibiose	.0088
Maltose	[3] .0072
Glucose	[6] .0065
Cellobiose	.0047
Lactose	[7] .0046

[1] Hudson and Yanovsky, recent unpublished measurement.
[2] Osaka's calculation (Z. physik. Chem., 35, 661; 1900) of Schnelle's results (Dissertation, Göttingen; 1891).
[3] Osaka's calculation from Parcus and Tollens' results (Ann., **257**, 160; 1890).
[4] Osaka's calculation from Günther and Tollens' results (Ibid., **271**, 90; 1892).
[5] Hudson and Sawyer, Jour. Am. Chem. Soc., **39**, 470; 1917.
[6] Hudson and Dale, Jour. Am. Chem. Soc., **39**, 320; 1917.
[7] Hudson, Z. physik. Chem., **44**, 487; 1903.

The initial and final solubilities of most of the crystalline sugars are summarized in the following table:

TABLE 13.—*Solubilities of sugars at 20°*

Sugar	Formula	Solvent	Grams of anhydrous sugar in 100 cc solution	
			Initial solubility	Final solubility
β-Arabinose	$C_5H_{10}O_5$	80 per cent alcohol	0.74	1.94
β-Cellobiose	$C_{12}H_{22}O_{11}$	20 per cent alcohol	3.2	4.7
β-Fructose	$C_6H_{12}O_6$	80 per cent alcohol	13.4	27.4
β-Fructose	$C_6H_{12}O_6$	95 per cent alcohol	1.8	4.2
β-Fructose	$C_6H_{12}O_6$	Methyl alcohol	5.2	11.1
α-Galactose	$C_6H_{12}O_6$	60 per cent alcohol	1.1	3.1
α-Galactose	$C_6H_{12}O_6$	80 per cent alcohol	.27	.65
β, α-Glucoheptose	$C_7H_{14}O_7$	20 per cent alcohol	4.0	4.5
α-Glucose	$C_6H_{12}O_6$	80 per cent alcohol	2.0	4.5
α-Glucose	$C_6H_{12}O_6$	Methyl alcohol	.85	1.6
α-Glucose hydrate	$C_6H_{12}O_6.H_2O$	80 per cent alcohol	1.3	3.0
β-Glucose	$C_6H_{12}O_6$	80 per cent alcohol	4.9	9.1
α-Lactose hydrate	$C_{12}H_{22}O_{11}H_2O$	40 per cent alcohol	1.1	2.4
α-Lyxose	$C_5H_{10}O_5$	60 per cent alcohol	5.4	7.9
β-Maltose hydrate	$C_{12}H_{22}O_{11}.H_2O$	60 per cent alcohol	3.0	4.75
β-Mannose	$C_6H_{12}O_6$	80 per cent alcohol	2.4	13.0
β-Mannose	$C_6H_{12}O_6$	Methyl alcohol	.78	4.4
β-Melibiose dihydrate	$C_{12}H_{22}O_{11}.2H_2O$	80 per cent alcohol	.76	1.3
α-Rhamnose hydrate	$C_6H_{12}O_5.H_2O$	Absolute alcohol	8.6	9.5
α-Rhamnose hydrate	$C_6H_{12}O_5.H_2O$	70 per cent alcohol	8.2	9.6
α-Xylose	$C_5H_{10}O_5$	80 per cent alcohol	2.7	6.2
Sucrose	$C_{12}H_{22}O_{11}$	80 per cent alcohol	3.7	3.7
Trehalose dihydrate	$C_{12}H_{22}O_{11}.2H_2O$	70 per cent alcohol	1.8	1.8
Raffinose pentahydrate	$C_{18}H_{32}O_{16}.5H_2O$	50 per cent alcohol	1.4	1.4

7. SOME NUMERICAL RELATIONS AMONG THE ROTATORY POWERS OF THE COMPOUND SUGARS [58]

The general group of polysaccharides includes many pure crystalline substances of definite chemical individuality, such as the di-, tri-, and tetra-saccharides, together with a series of amorphous products, such as starch, glycogen, inulin, cellulose, pentosans, mannans, galactans, etc. To distinguish the pure crystalline polysaccharides from their less definitely characterized relatives, it is suggested that they be classed under the group name of compound sugars, a designation which separates them very well also from the simple sugars, or monosaccharides, into which they may be decomposed by hydrolysis. In the present article, it is sought to extend to several of the compound sugars the numerical relationships that have been found to hold among the rotatory powers of the α and β forms of the monosaccharides and their glucosidic derivatives.[59]

(a) SUGARS OF THE SUCROSE GROUP

(1) KNOWN MEMBERS OF THE GROUP.—The trisaccharide raffinose may be split by complete hydrolysis into its three component simple sugars, galactose, glucose, and fructose; by partial hydrolysis, best through the agency of enzyme action, it may be split either into fructose and melibiose (=galactose<glucose<[60]) by the use of invertase or weak acids, or into galactose and sucrose (=*glucose*<>*fructose*) by the aid of emulsin. Raffinose may accordingly be regarded as *galactose*<*glucose*<>*fructose*, a derivative of sucrose, a combination between that sugar and galactose. Other sugars which are now regarded as derivatives of sucrose are[61] gentianose (=*glucose*<*glucose*<>*fructose*) and stachyose (=*galactose*<*galactose*<*glucose*<>*fructose*). It will be convenient to designate sucrose and its three derived compound sugars as members of the sucrose group. The evidence that gentianose and stachyose belong in the group is not direct and conclusive as in the case of raffinose, though it appears convincing, as will be seen. The action of invertase upon either sucrose or raffinose causes specific hydrolysis of the union between glucose and fructose, which may be designated the "sucrose union." Invertase may be regarded, therefore, as a specific hydrolyst of the "sucrose union," and the action of this enzyme upon a compound sugar may be taken as evidence that the sugar contains the "sucrose union" and is a derivative of sucrose. Bourquelot and Hérissey[62]

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[58] Quoted from Hudson, J. Am. Chem. Soc., **38**, 1566; 1916.

[59] J. Am. Chem. Soc., **31**, 66; 1909.

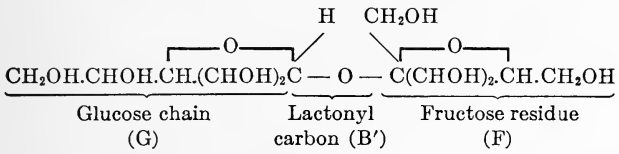
[60] The symbol < denotes the carbonyl or lactonyl group. See J. Am. Chem. Soc., **31**, 661; 1909. The term lactonyl, which has been suggested by S. F. Acree (Science, **42**, 101; 1915) to indicate an aldehyde or ketone group that has formed a lactone-like ring, as in the sugars, seems very appropriate.

[61] Bourquelot and Bridel, Compt. rend., **152**, 1060; 1911.

[62] J. pharm. chim., [6], **13**, 305; 1901.

have shown that invertase splits gentianose into fructose and gentiobiose (=*glucose*<*glucose*<) and C. Tanret[63] has shown that it splits stachyose into fructose and manninotriose (=*galactose*<*galactose*<*glucose*<), hence these sugars are considered to be derivatives of sucrose. Recently Bourquelot and Bridel[64] have isolated a new crystalline compound sugar, verbascose, which is hydrolyzed by invertase to fructose and another sugar, not yet isolated; probably verbascose belongs in the sucrose group.

(2) Rotatory Relationships in the Sucrose Group.—The fact that sucrose is not a reducing sugar indicates that the lactonyl hydroxyl groups of its two constituents are bound in glucosidic union, and the further fact that only one molecule of water per molecule of sucrose becomes combined during hydrolysis shows that the groups in question are joined with each other, because if the union were otherwise, two molecules of water per molecule of sugar would be used up. The same conclusion may be drawn from the fact that sucrose yields an octa-acetate and contains, therefore, eight hydroxyl groups per molecule. The structure of sucrose is accordingly generally considered to be



In this formula it is assumed that the lactonyl ring is upon the γ carbon of both hexoses, which appears likely, but the following argument would not be affected if these rings should prove to be in other positions:[65] Let G represent the rotation due to the glucose chain, not including, however, the asymmetric lactonyl carbon of rotation B', and let F be the rotation of the fructose residue. Summing these values the molecular rotation of sucrose may be written $[M]_s = G+B'+F$. According to this plan the molecular rotations of the members of the sucrose group may be formulated as follows, when (*Mb*), (*Gb*), and (*Mn*) indicate the rotations of the melibiose, gentiobiose, and manninotriose chains, respectively:

Parent sugar	Hydrolytic products with invertase	Molecular rotation of the parent sugar
Sucrose (M. W. 342)	Glucose (180)+fructose (180)	$G+B'+F$ (1).
Raffinose (504)	Melibiose (342)+fructose	$(Mb)+B'+F$ (2).
Gentianose (504)	Gentiobiose (342)+fructose	$(Gb)+B'+F$ (3).
Stachyose (666)	Manninotriose (504)+fructose	$(Mn)+B'+F$ (4)

[63] Bull. soc. chim., **27**, 955; 1902. *See also* Vintilesco, J. pharm. chim., **30**, 167; 1909.

[64] Compt. rend., **151**, 760; 1910.

[65] What really is assumed, as will be understood from the continuation, is that the glucose lactonyl ring in sucrose is upon the same carbon atom as in the case of the α and β forms of glucose.

Subtracting the molecular rotation of sucrose from that of raffinose, $[M]_R$, gives

$$[M]_R - [M]_S = (Mb) - G \quad (5)$$

The specific rotation of sucrose is +66.5, and its molecular rotation (66.5) (342) = +22,700 = $[M]_S$. In the article first cited it was shown that G may be obtained as half the sum of the molecular rotations of the α and β forms of glucose, which gives the value +11,900 if the specific rotations of the two forms of glucose are taken as 113 and 19.[66] Introducing these values in equation (5) and transposing gives

$$(Mb) = [M]_R - 10{,}800 \quad (6)$$

To pass now from (Mb) to the rotation of either the α or β form of melibiose it is necessary to add the rotation of the end asymmetric lactonyl carbon atom of melibiose. It has been shown in the former article that the rotation of this carbon is equal to half the difference of the molecular rotations of the α and β forms of glucose, or 8,460, hence the molecular rotations of the forms of melibiose are written:

Molecular rotation of α-melibiose = $(Mb) + 8{,}460 = [M]_R - 2{,}340$
Molecular rotation of β-melibiose = $(Mb) - 8{,}460 = [M]_R - 19{,}300$

Similar equations with the same numerical terms express the same relation between the molecular rotations of gentiobiose and gentianose, and of manninotriose and stachyose. For the sugars of the sucrose group that are hydrolyzed by invertase to yield fructose and an aldose, the molecular rotation of the aldose is less than that of its parent sugar by 2,340 for its α form and 19,300 for its β modification. The rotatory powers of melibiose, gentiobiose, and manninotriose may be calculated by this relation.

(3) The Rotation of Melibiose.—Since the specific rotation of raffinose is +123, its molecular rotation is +62,000, and the molecular rotations of the α and β forms of melibiose are calculated from the foregoing relation to have the values +59,700 and +42,700, respectively, and from these the specific rotations are found to be +175 and +125°. The latter value agrees almost exactly with Loiseau's[67] measurement of the initial specific rotation of β-melibiose (124), and recently E. Yanovsky and the writer, in repeating the measurement, have obtained the same value as Loiseau. The α form of melibiose has never been prepared in a pure state and the only experimental value known for its specific rotation is that which Yanovsky and the author have found indirectly through a measurement of the increase in solubility of β-melibiose during its mutarotation. (See p. 269). Our value is +179°. The agreement is very good in view of the indirectness of the experimental measurement.

[66] Hudson and Yanovsky, J. Am. Chem. Soc., **39**, 1035; 1917.
[67] Z. Ver. Zuckerind., **52**, 1050–1059; 1903.

(4) The Rotation of Gentiobiose.—The specific rotation of gentianose is $+31$,[68] hence its molecular rotation is $+15{,}600$ and the specific rotations of the α and β forms of gentiobiose may be calculated by the method which has just been followed to be $+39$ and -11, respectively. Bourquelot and Hérissey[69] record $+9.8$ as the final specific rotation of gentiobiose, a value which refers to the equilibrium in solution between the α and β forms of the sugar. By crystallizing gentiobiose from methyl alcohol they obtained a crystalline derivative of it containing two molecules of methyl alcohol of crystallization. This substance had an initial specific rotation in water of about $+18$, decreasing to $+9.8$ (both numbers are referred to the solvent-free sugar, m. w. 342) on standing. By crystallizing gentiobiose from ethyl alcohol solution they prepared the crystalline sugar itself, which had a specific rotation of -6 six minutes after dissolving, changing likewise to $+9.8$ on standing. If one extrapolates as well as possible the value -6 back through the first six minutes according to the rate of mutarotation that Bourquelot and Hérissey observed, a value near the calculated -11 is obtained. It would seem that the α form of gentiobiose which they evidently had in hand in the form of a compound with methyl alcohol of crystallization contained some of the β modification.

(5) The Rotation of Manninotriose.—The specific rotation of stachyose being $+148$,[70] its molecular rotation is $+98{,}600$, and hence the specific rotations of the α and β forms of manninotriose are calculated to be $+191$ and $+157$, respectively. These rotations do not appear to have ever been measured, but C. Tanret[71] records $+167$ as the final specific rotation of manninotriose. This value lies between the calculated numbers, as should be the case, and is also at approximately the same position between them as in the case of glucose, melibiose, and gentiobiose. The ratio of the concentrations of the β and α forms which are present at equilibrium is for glucose $(113-52)/(52-19)=1.8$, for melibiose $(175-143)/(143-124)=1.6$, for gentiobiose $(39-10)/(10+11)=1.3$, and for manninotriose $(191-167[72])/(167-157)=2.4$. If the final rotation of manninotriose were 169 rather than 167 the ratio would be the same as for glucose, and if it were 172 the ratio would be the same as for gentiobiose.

(6) Other Possible Members of the Sucrose Group.—Since lactose, cellobiose and maltose have structures in which the free lactonyl hydroxyl is a part of the glucose group, it is conceivable that these disaccharides might be united with fructose through a

[68] Bourquelot and Nardin, Compt. rend., **126**, 280; 1898.
[69] J. pharm. chim., 6, **16**, 418; 1902.
[70] Schulze and Planta, Ber., **24**, 2705; 1890.
[71] Bull. soc. chim., 3, **29**, 891; 1903.
[72] Final specific rotation of the sugar.

sucrose union to yield derivatives of sucrose. The expected specific rotations of these compounds can be calculated according to the preceding considerations. For example, since the specific rotation of β-lactose (m. w. 342) is $+35$, its molecular rotation is $+12{,}000$, and the specific rotation of the hypothetical *α-lactose < > α-fructose* (m. w. 504) is calculated to be $(12{,}000+19{,}300)/504=+62$.

(7) THE ACETYLATED SUGARS OF THE SUCROSE GROUP.—Referring back to the structural formula for sucrose, consider the rotation of sucrose octa-acetate. Its molecular rotation is the sum of a new quantity G', which is the rotation of an acetylated glucose chain, plus B'', which may possibly be different in value from B', plus F', the rotation of an acetylated fructose residue. In the same way that G was obtained from the specific rotations of the α and β forms of glucose G' may be found from those of the corresponding glucose penta-acetates (m. w. 390), which have the values $+102$ and $+4$, respectively, in chloroform solution.[73] Half of the sum of their molecular rotations is $+20{,}700=G'$, and half the difference is $+19{,}100$, the latter being the rotation of the end asymmetric carbon in glucose penta-acetate. The specific rotation of sucrose octa-acetate (m. w. 678) in chloroform is $+59.6$,[74] and hence its molecular rotation is $+40{,}400$. The molecular rotation of the glucose penta-acetate chain is therefore 19,700 less than that of sucrose octa-acetate or the molecular rotations of α-glucose penta-acetate is $(19{,}700-19{,}100)=600$ less than that of sucrose octa-acetate, while that of the β-penta-acetate is $(19{,}700+19{,}100)=38{,}800$ less. These numerical differences apply also to the molecular rotations of the corresponding acetylated derivatives of the pairs raffinose and melibiose, gentianose and gentiobiose, stachyose and manninotriose. The β octa-acetates (m. w. 678) of melibiose and gentiobiose have the specific rotations $+102$[75] and -5,[76] respectively, in chloroform solution. From these data the specific rotations of the hendeca-acetates (m. w. 966) and formula $C_{28}H_{21}(C_2H_3O)_{11}O_{16}$) of raffinose and gentianose in chloroform are calculated to be $+112$ and $+43$, respectively. Scheibler and Mittelmeier [77] have found $+92$ for crystalline raffinose hendeca-acetate in alcohol, but the value in chloroform is not known. It is probably higher than $+92$, because the specific rotation of sucrose octa-acetate in chloroform is $+60$ (see preceding) and in alcohol, $+38$.[78] Gentianose hendeca-acetate does not appear to have ever been prepared.

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[73] Hudson and Dale, Jour. Am. Chem. Soc., **37**, 1265; 1915.
[74] Hudson and Johnson, Jour. Am. Chem. Soc.. **37**, 2753; 1915.
[75] Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 2752; 1915.
[76] Zemplén, Z. physiol. Chem., **85**, 402; 1913.
[77] Ber., **23**, 1443; 1890.
[78] Herzfeld, Ber., **13**, 267; 1880.

(b) SUGARS OF THE TREHALOSE GROUP

(1) TREHALOSE AND ISOTREHALOSE.—Since trehalose is not a reducing sugar, combines with only one molecule of water per molecule of sugar during hydrolysis, and also forms an octa-acetate, its structure may be considered to be *glucose*< >*glucose*, the lactonyl hydroxyls being united with the elimination of water. The three possible combinations which fit this structure, assuming γ–lactonyl rings, are *α-glucose*< >*α-glucose*, the α,β form, or the β,β form. If G represents the rotation of the glucose chain, as before, and A' that of the asymmetric lactonyl carbon ($+A'$ for the α-glucoside form and $-A'$ for the β) the molecular rotations of the three combinations may be formulated:

α, α-Trehalose ..... $G+A'+A'+G=2G+2A'$
α, β-Trehalose ..... $G+A'-A'+G=2G$
β, β-Trehalose ..... $G-A'-A'+G=2G-2A'$

The value of $2G$ has already been found from the sum of the molecular rotations of the α and β forms of glucose to be +23,800, and hence the specific rotation of α,β-trehalose (m. w. 342) is calculated to be +70. This value is entirely different from the observed specific rotation of trehalose, +197, hence the natural sugar is not the α,β combination. Neither can it be the β,β form because it should then be less dextrorotatory than +70 since the value of $-A'$ for the known β-glucosides is a quantity of considerable magnitude. On the other hand, the high dextrorotation of trehalose agrees well with what would be expected for *α-glucose*< >*α-glucose*. Assuming this to be the structure of the natural sugar, its molecular rotation ($197\times342=+67{,}400$) is $2G+2A'$, and since $2G$ is +23,800, $2A'$ is +43,600, and the molecular rotation of β,β-trehalose ($2G-2A'$) may be calculated to be −19,800, and the specific rotation −58. Under the name *isotrehalose*, Fischer and Delbrück [79] have recently described a sugar of the trehalose type which they prepared by the saponification of crystalline *isotrehalose octa-acetate*, a substance which in its turn was made by the condensation of bromo-acetyl glucose. Isotrehalose was not obtained in a crystalline state and the amorphous substance was not free from ash. Under such conditions the specific rotation of the impure material can only be considered as an approximate value of the rotation of the pure sugar. Fischer and Delbrück found −39, a value which strongly suggests that isotrehalose is β,β-trehalose. This view is supported by the fact that all other derivatives that have been prepared from bromo-acetyl glucose belong to the β series. It is also supported by the result of the following considerations, which indicate that the parent substance, *isotrehalose octa-acetate*, is a β,β form.

[79] Ber., **42**, 2776; 1909.

(2) Octa-acetates of the Trehalose Sugars.—The relations which have just been derived among the rotations of the three trehaloses and the α and β forms of glucose apply likewise to the fully acetylated derivatives of these five substances. Thus the molecular rotation of α, β-trehalose octa-acetate may be regarded equal to the sum of the molecular rotations of the α and β glucose penta-acetates, which is known to be $+41{,}400$, and its specific rotation (m. w. 678) in chloroform is calculated to be $+61$. The observed specific rotation of pure trehalose octa-acetate in chloroform is $+162$,[80] which indicates again that trehalose is the α, α form. The specific rotation of the β, β form, or isotrehalose octa-acetate, is calculated from these two rotations, by the same method that was used with the sugars, to be -40 in chloroform. Fischer and Delbrück found -17 in benzene, a difference which may be due to the change of solvent, because trehalose octa-acetate rotates $+162$ in chloroform and $+171$ in benzene.[81]

(3) Other Compound Sugars of the Trehalose Type.—It may be useful to indicate that the rotation of nearly all the possible sugars of this type may be calculated from existing data. As an illustration consider the tetra-saccharide *lactose*< >*lactose* a combination which E. Fischer and H. Fischer[82] have sought to prepare through the condensation of bromoacetyl lactose. Since the α and β forms of lactose (m. w. 342) rotate $+86$ and $+35$, respectively, twice the molecular rotation of the lactose chain is $+41{,}400$. Since the molecular weight of the tetra-saccharide is 666, the specific rotation of its α, β form is calculated to be $41{,}400/666 = +62$. Assuming that the asymmetric lactonyl carbons uniting the glucose residues have the same rotations that were found for them in trehalose, $2A' = +44{,}000$ and hence the specific rotation of the α, α form of the tetra-saccharide is calculated to be $(41{,}400 + 44{,}000)/666 = +128$, and that of the β, β form $(41{,}400 - 44{,}000)/666 = -4$.

From the specific rotations of the α and β lactose octa-acetates (m. w. 678), $+54$ and -4 in chloroform[83] and the value $+68{,}500$ for the two lactonyl carbons (calculated as in the case of the trehalose octa-acetates), the specific rotation of the fully acetylated derivatives (m. w. 1,255) of *lactose*< >*lactose* may be calculated to be, for the α, β form $+33{,}900/1{,}255 = +27$, for the α, α form $(33{,}900 + 68\,500)/1{,}255 = +82$, for the β, β form -28. The similar derivatives of maltose and cellobiose can be treated in the same way. The calculations are here indicated because the work of E. Fischer with H. Fischer, and Zemplen[84] appears to open a way for synthesizing these compounds of lactose, maltose and cellobiose, respectively, when sufficient material is available.

[80] Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 2752; 1915.
[81] Measured recently in this laboratory by Dr. J. M. Johnson.
[82] Ber., **43**, 2532; 1910.
[83] Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 1273; 1915.
[84] Ber., **43**, 2536; 1910.

Lastly, the expected specific rotation of *β,l-arabinose* < > *β,l-arabinose* (m. w. 282) may be calculated from the specific rotations of the *α* and *β* forms of the sugar, +76 and +184, respectively, to be ((+76+184) 150+44,000[85]) /282 = +294°. This rotation is of interest because it appears to be the largest specific rotation that can be expected among the sugars from present data.

(c) THE RELATED ROTATIONS OF LACTOSE AND CELLOBIOSE

There are three disaccharides which have the general structure *glucose* < *glucose* <, namely maltose, cellobiose and gentiobiose, and two of the composition *galactose* < *glucose* <, namely, melibiose and lactose. In these structures the place of attachment of the left-hand glucose or galactose molecule is evidently its lactonyl carbon, but several points of union for the right-hand glucose molecule are possible. Without more knowledge of this point of attachment for each of the compound sugars, it does not seem possible, in general, to obtain relations among their rotatory powers. However, there is one special case which can be adequately treated at present and it leads to an interesting relation between the rotations of lactose and cellobiose. The structures shown above indicate that for each point of attachment in the right-hand glucoside residue, there can be four related sugars according as the left-hand member is *α*- or *β*-glucose, or *α*- or *β*-galactose. To formulate the rotations of these forms let *G* and *Ga*, respectively, be the rotations of the left-hand glucose and galactose chains, *L* that of their bound lactonyl carbons, and *R* that of the common right-hand glucose residue. Since the free lactonyl group of this residue permits *α* and *β* forms, let *R* refer throughout to the same one of these. The molecular rotations of the four structures are thus:

α-galactose<glucose< = $Ga+L+R$	*β*-galactose<glucose< = $Ga-L+R$
α-glucose<glucose< = $G+L+R$	*β*-glucose<glucose< = $G-L+R$
Difference $Ga-G$	$Ga-G$

The differences are equal to each other, and as will be seen readily are also equal to the difference of the molecular rotations of the corresponding *α* and *β* forms of galactose and glucose, or of methyl galactoside and methyl glucoside. We reach the conclusion, therefore, that if either of the *galactose* < *glucose* < sugars (melibiose or lactose) has a structure in which the right-hand glucose residue is identical with the similar component of one of the *glucose* < *glucose* < sugars (maltose, cellobiose or gentiobiose) the pair of sugars, in case both are *α*-glucosidic compounds or both *β*, should differ in molecular rotation by the difference between the molecular rotations of the galactose and glucose chains. The difference in specific rotation of *β*-methyl galactoside (0°) and *β*-methyl glucoside (−32°) (of m. w. 194) is +32°, which amounts to (32) (194)/342 = +18° in the specific

[85] The assigning of a positive rather than negative sign to 44,000 (= 2*A*), although the compound is a *β*-derivative, is made because the arabinose is the levo form. See Jour. Am. Chem. Soc., **31**, 72; 1909.

rotation of the disaccharides (m. w. 342). If +18 be added to the specific rotation of the β forms of maltose (+118) and of gentiobiose (−11) the sums, +136 and +7 do not agree with the rotations of either β-melibiose (+124) or β-lactose (+35). On the other hand, the rotation of β-cellobiose (+16)[86] plus 18 is equal to that of β-lactose (35) almost exactly.

(1) The Rotations of the Octa-acetates of These Sugars.—It is highly desirable to test in independent ways this conclusion, that lactose and cellobiose have the same structure for their common glucose residue, and that the galactose residue of one belongs to the same series (probably the β, judging from the low rotation of lactose) as the glucosidic glucose residue of the other. If the similarity does exist, it would be expected to extend to many derivatives of these sugars, and it should be possible to decide from a comparison of the rotations of each pair of derivatives whether the agreement that has been found to hold for the parent sugars is a general one and really has for its basis the assigned reason, or is an accidental agreement in the one case tested. The rotations in chloroform solution of the pure octa-acetates of the disaccharides in question are known, and a comparison of them appears to be of special value because in them the rotations of the individual asymmetric carbon atoms in the glucose residue are doubtless quite different from the values for the sugars themselves. The difference between the specific rotations of tetra-acetyl β-methyl galactoside (−13), of m. w. 362, and the corresponding acetylated β-methyl glucoside (−18)[87] is +5, which corresponds to (5) (362)/678 = 3° for the disaccharide octa-acetates. The addition of this value to the specific rotation of β-maltose octa-acetate (+63) gives a sum entirely different from the rotation of the β-octa-acetate of either melibiose (+102) or lactose (−4). On the other hand, the rotations of the β-octa-acetates of both cellobiose (−15) and gentiobiose (−5) yield sums (−12 and −2) which are near the rotation of β-lactose octa-acetate (−4). The combination of this result with that obtained from the rotations of the sugars themselves, in which gentiobiose was clearly ruled out, gives strong evidence that the common glucose residues of lactose and cellobiose have identical structure.

8. A RELATION BETWEEN THE CHEMICAL CONSTITUTION AND THE OPTICAL ROTATORY POWER OF THE LACTONES OF THE SUGAR GROUP. THE LACTONE RULE OF ROTATION[88]

(a) THE HYPOTHESIS

The numerous sugars are strongly rotatory. On the other hand, the alcohols which result from their reduction and the acids which are formed by their oxidation are only feebly rotatory. But the gluco-

[86] Hudson and Yanovsky, Jour. Am. Chem. Soc., **39**, 1035; 1917.
[87] Hudson and Dale, Jour. Am. Chem. Soc., **37**, 1265; 1915.
[88] Quoted from Hudson, Jour. Am. Chem. Soc., **31**, 338; 1910.

sidic compounds of the sugars and the lactones of these acids are as strongly rotatory as the sugars themselves. Thus, for example, the specific rotations of the two forms of glucose are 109 and 20, of the methyl glucosides 157 and −32, of gluconic acid lactone 68, but the rotation of gluconic acid is only −2, and sorbitol, which is the alcohol that results from the reduction of glucose, shows almost no rotation. Is there any other property of these substances which varies in the same manner as the rotatory power?

The constitutional chemical formulas now in use for these compounds have been chosen step by step to express their chemical reactivities, and it is now generally agreed that the sugars, the glucosides and the lactones, possess a lactonic ring, but that this is absent from the structure of the alcohols and acids. Here, then, is a property, namely, the chemical constitution, which runs exactly parallel with the physical property of optical rotation in the case of the sugar glucose. Does the same parallelism hold for the other sugars?

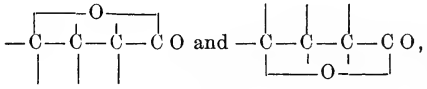
To answer this question reference may be made to Table 14, which gives the specific rotations of the principal aldose sugars, and their glucosidic, lactonic, acidic, and alcoholic derivatives, so far as they are known; the numerical values are in all cases quoted from the literature.

TABLE 14.—*Specific rotations of aldose sugar derivatives*

Sugars	$[\alpha]_D$	Glycosides	$[\alpha]_D$	Lactones	$[\alpha]_D$	Acids	Alcohols	$[\alpha]_D$
d-Glucose	α109 β52	Methyl	α157 β-32	Gluconic	68	−2	Sorbitol	0
d-Galactose	α140 β53	Methyl	α196 β0	Galactonic	−72	−11	Dulcitol	0
d-Arabinose	105	Benzyl	215	Arabonic	−74	−8	Arabitol	0
d-Mannose	α76 β-14	Methyl	79	Mannonic	54	(?)	Mannitol	0
d-Xylose	α100 β-8	Methyl	α152 β-66	Xylonic	83	−7	Xylitol	0
l-Rhamnose	α<-7 β>31	Methyl	−62	Rhamnonic	−35	−8	Rhamnitol	11
l-Ribose	(?)	(?)		Ribonic	−18	(?)	Adonitol	0
d-Mannoheptose	85	(?)		Mannoheptonic	−74	(?)	Mannoheptitol	−1
Rhodeose	86	Ethyl	30	Rhodeonic	−76	(?)	(?)	
d-Talose	(?)	(?)		Talonic	−Strong.	(?)	Talitol	0.2
d-Gulose	(?)	(?)		Gulonic	−55	(?)	Sorbitol	0
α-Galaheptose	(?)	(?)		α-Galaheptonic	−52	(?)	α-Galaheptitol	0
β-Galaheptose	−22	(?)		β-Galaheptonic	(?)	(?)	(?)	
α-Gluco-octose	−51	(?)		α-Gluco-octonic	46	(?)	α-Gluco-octitol	2
d-Mannononose	50	(?)		Mannonononic	−41	(?)	(?)	
d-Gala-octose	−40	(?)		Gala-octonic	64	(?)	(?)	

The data show that the sugars, the glycosidic compounds, and the lactones, all of which contain the lactonic ring, have strong rotatory powers. There are three apparent exceptions, β-methyl galactoside, β-xylose, and α-rhamnose, but for each of these the corresponding α or β isomer is strongly rotatory, proving that the slight rotations of the three compounds are due to internal compensations, and that they contain strongly active carbon atoms. On the other hand, the alcohols and acids are of feeble rotatory powers, which are, in general, not comparable with the strong rotations of the sugars, glucosidic compounds and lactones. There is thus satisfactory proof that the lactonic ring structure causes a strong rotation.

The rotations of the alcohols and acids recorded are so small in comparison with those of the lactones that the rotations of the latter may be assumed to be due, as a first approximation, entirely to the lactonic ring. There are two possible stereo structures for the lactonic ring, namely



which are mirror images (with the mirror placed horizontally). If the rotation of the lactone is due entirely to this ring, the position of the ring must determine the sign of the rotation of the lactone. The position of the ring is determined by the position which the OH group had on the γ-carbon atom before the ring was formed. These ideas thus lead to the following hypothesis: Lactones of dextrorotation have the lactonic ring on one side of the structure, lactones of levorotation have it on the other, and the position of the ring shows the former position of the OH group on the γ-carbon atom.

(b) TEST OF THE HYPOTHESIS

This hypothesis will now be tested. In Table 15 there are collected the structural formulas and specific rotations of 24 lactones of the monobasic sugar acids, including every such lactone for which the structure and specific rotation have been determined. The first column gives the name and the second the stereo configuration of the lactone, the discovery of which is due in all cases to the immortal researches of Emil Fischer. In the third column is the statement, for convenience, of the position of the lactonic ring, whether "above" or "below" the chain, and in column 4 are the specific rotations of the lactones, which are quoted from Lippmann's "Chemie der Zuckerarten." In most cases they were measured by Emil Fischer or his students.

TABLE 15.—*Parallelism between the sign of the rotation and the configuration of the sugar lactones*

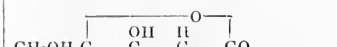
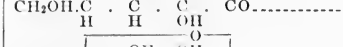
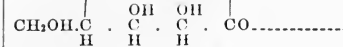
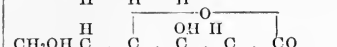
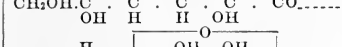
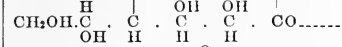
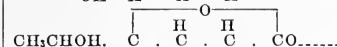
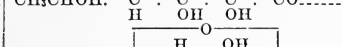
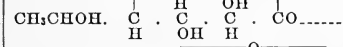
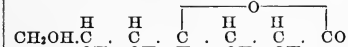
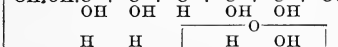
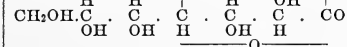
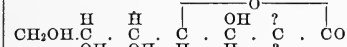
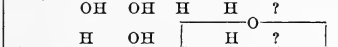
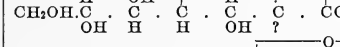
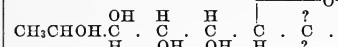
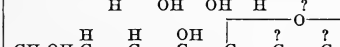
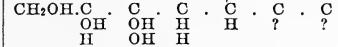
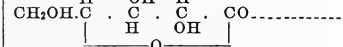
Lactone	Fischer's configuration	Ring position	Specific rotation
l-Arabonic		Above	−74
l-Ribonic		do	−18
d-Galactonic		do	−78
d-Talonic		do	−(?) Large
l-Rhamnonic		do	−39
l-Isorhamnonic		do	−62
d-α-Glucoheptonic		do	−55
d-β-Glucoheptonic		do	−68
d-Mannoheptonic		do	−74
d-Galaheptonic		do	−52
l-Rhamno-octonic		do	−51
d-Manno-octonic		do	−44
d-Xylonic		Below	+83
d-Lyxonic		do	+82
d-Gluconic		do	+68
d-Mannonic		do	+54
l-Gulonic		do	+56
l-α-Rhamnohexenic		do	+84
l-β-Rhamnohexonic		do	+43

TABLE 15.—*Parallelism between the sign of the rotation and the configuration of the sugar lactones*—Continued

Lactone	Fischer's configuration	Ring position	Specific rotation
l-α-Rhamnoheptonic	$CH_3CHOH.\overset{OH}{H}C.\overset{H}{OH}C.\overset{H}{OH}C.\overset{OH}{H}C.\overset{?}{H}C.CO$ (O)	Below	+56
d-α-Gluco-octonic	$CH_2OH.\overset{H}{OH}C.\overset{H}{OH}C.\overset{OH}{H}C.\overset{H}{OH}C.\overset{H}{OH}C.\overset{?}{OH}C.CO$ (O)	do	+46
d-β-Gluco-octonic	$CH_2OH.\overset{H}{OH}C.\overset{H}{OH}C.\overset{OH}{H}C.\overset{H}{OH}C.\overset{H}{OH}C.\overset{?}{OH}C.CO$ (O)	do	+24
d-α-Gala-octonic	$CH_2OH.\overset{H}{OH}C.\overset{OH}{H}C.\overset{OH}{H}C.\overset{H}{?}C.\overset{?}{?}C.CO$ (O)	do	+64
d-α-Gluco-nononic	$CH_2OH.\overset{H}{OH}C.\overset{H}{OH}C.\overset{OH}{H}C.\overset{H}{OH}C.\overset{H}{?}C.\overset{?}{?}C.CO$ (O)	do	+(?) Large

The table shows that among these 24 aldonic lactones (which include all the known substances for which there are sufficient data known to test the hypothesis) there is not a single exception to the theory, all the lactones which have the ring "above" the chain are levorotatory and all having it "below" the chain are dextrorotatory.

(c) APPLICATION OF THE THEORY TO DETERMINE THE CONFIGURATIONS OF THE SUGARS

As this relation between the stereoposition of the lactonic ring and the sign of the rotation of the lactone is well founded, it may be used in determining the configurations of the sugars. For some of the sugars such a determination is only a tracing backward of the steps of the above experimental proof of the hypothesis, but for certain others (for example, rhamnose) this method gives entirely new data on the constitution, as will be shown. In determining the constitutions and configurations of the sugars Emil Fischer has used most ingeniously a mass of chemical data of various kinds, nearly all of which he worked out in his own laboratory. In what follows it will be shown that the configurations of the monose aldehyde sugars can be independently determined from two kinds of experimental data: (1) A knowledge of the sugars which result from the cyanide synthesis or its reverse; and (2) a knowledge of the signs of the rotations of the lactones of the aldonic acids. This second kind of data can not be obtained for the ketone sugars, because they do not yield acids and lactones, and their configurations can not be found by this method.

(1) THE STEREOCONFIGURATION OF *d*-GLUCOSE.—The cyanide synthesis or its reverse has shown the steps of the following series: *d*-erythrose → *d*-arabinose → *d*-glucose → *d*-glucoheptose → *d*-gluco-octose. The specific rotations of the lactones of the monobasic acids

derived from these sugars are (see Table 15), *d*-arabonic +74, *d*-gluconic +68, *d*-glucoheptonic −68, *d*-gluco-octonic +46. Writing the carbon chain of the octose

$$\left[\underset{}{CH_2OH}.\ \underset{(1)}{C}\ .\ \underset{(2)}{C}\ .\ \underset{(3)}{C}\ .\ \underset{(4)}{C}\ .\ \underset{(5)}{C}\ .\ \underset{(6)}{C}\ .\ \underset{(7)}{C}\right]$$

it is first noticed that as its lactone rotates positive (+46) its ring is to be considered as below the chain and joining atom 7 to its γ-carbon 4. This shows that the hydrogen atom on 4 is above the chain. Passing next to the heptose, since its lactone rotates negative (−68) the hydrogen atom on the new γ-carbon 3 by the same reasoning is below the chain. Similarly the signs of the rotations of the other two lactones show that the hydrogen atom is above 2 and above 1. This determines the stereoconstitution of the carbons 1, 2, 3, and 4, and as these are all the asymmetric carbons which occur in the aldehyde formula of glucose, this may be written as follows:

$$CH_2OH.\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ COH\ .$$

This formula is identical with the one which Emil Fischer has chosen from chemical data alone. The steps of this proof of the structure of *d*-glucose give also the structures of *d*-arabinose and *d*-erythrose.

(2) The Stereoconfiguration of *d*-Galactose.—The cyanide synthesis or its reverse has shown the following series: *d*-lyxose → *d*-galactose → *d*-galaheptose → *d*-gala-octose, and the rotations of the lactones of the corresponding monobasic acids have been found to be (Table 15) *d*-lyxonic +82, *d*-galactonic −78, *d*-galaheptonic −52, *d*-gala-octonic +64. By the same reasoning as given under the preceding section these rotations show that in the stereoformula of galactose the hydrogen atom is above carbons 1 and 4 and below 2 and 3, giving,

$$CH_2OH.\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ COH\ .$$

This formula is identical with the one which Fischer has chosen for galactose. The stereoconfiguration of d-lyxose follows from that of *d*-galactose.

(3) The Stereoconfiguration of *d*-Mannose.—The cyanide reaction has shown the following series: *d*-arabinose → *d*-mannose → *d*-mannoheptose → *d*-manno-octose, and the rotations of the lactones of the corresponding monobasic acids have been found to be (Table 15), *d*-arabonic +74, *d*-mannonic +54, *d*-mannoheptonic −74, *d*-manno-octonic −44. In the configuration of mannose, therefore, the hydrogen atom is below 3 and 4 and above 1 and 2, giving,

$$CH_2OH.\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ COH\ .$$

This is also identical with the structure which Fischer has established for mannose.

(4) THE STEREOCONFIGURATION OF RHAMNOSE.—This methyl pentose sugar has been shown by Fischer to have the stereoconfiguration

$$CH_3CHOH.\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ COH$$

but he was unable to obtain any data which would establish the stereostructure of the first group CH_3CHOH. This physico-chemical method for establishing the structure of the sugars can be applied in this case where the usual strictly chemical methods fail. Writing the carbon chain for rhamnose

$$\left[CH_3\ .\ \underset{(1)}{C}\ .\ \underset{(2)}{C}\ .\ \underset{(3)}{C}\ .\ \underset{(4)}{C}\ .\ \underset{(5)}{C}\right]$$

and referring to the following cyanide syntheses, methyl tetrose→ rhamnose → rhamnohexose → rhamnoheptose, the specific rotations of the corresponding lactones having been found by Fischer to be methyl tetronic −47, rhamnonic −35, rhamnohexonic +84, and rhamnoheptonic +56, it is seen that the hydrogen atom is to be placed above carbons 3 and 4 and below 1 and 2, yielding the following configuration for rhamnose,

$$CH_3\ .\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ \begin{matrix} H \\ C \\ OH \end{matrix}\ .\ COH$$

This agrees with Fischer's structure for the atoms 2, 3, and 4, and it also shows the configuration of atom 1, which has been in doubt. Rhamnose is thus a reduction product from *l*-mannose.[89] It is interesting to note that Winther[90] has previously selected this configuration for the first carbon, basing his selection upon the fact that Tate's bacillus attacks rhamnose.

(5) PARTIAL STEREOCONFIGURATIONS OF RHODEOSE AND FUCOSE.—The methyl pentose rhodeose yields a lactone with the specific rotation −76,[91] consequently its structure can be partially determined from the above principles to be

$$CH_3\ .\ \begin{matrix} | \\ C \\ | \end{matrix}\ .\ \begin{matrix} OH \\ C \\ H \end{matrix}\ .\ \begin{matrix} | \\ C \\ | \end{matrix}\ .\ \begin{matrix} | \\ C \\ | \end{matrix}\ .\ COH$$

and it follows that its antipode, fucose, is the mirror image of this.

(d) PROOF OF THE POSITION OF THE LACTONIC RING

The foregoing relations furnish a proof of a view which organic chemists have been led to adopt by a large number of chemical facts, namely, that the formation of lactones involves the γ-carbon atom

[89] The configuration here shown for rhamnose was subsequently proved from chemical syntheses by Fischer and Zach, Ber., **45**, 3761; 1912.

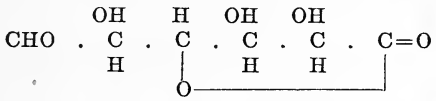
[90] Ber., **28**, 3000; 1895.

[91] Votoček, Zts. Zucker-Ind. (Böhmen), **25**, 297; 1902.

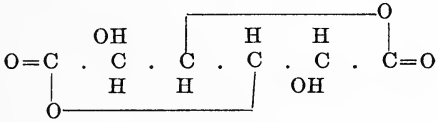
preferably to any other. The parallel relation between the position of the lactonic ring and the sign of the rotation of the lactone is based on the assumption that the ring is formed on the γ-carbon atom; if it were considered as formed on any other atom whatsoever the parallelism would no longer hold even approximately; thus, referring back to Table 15, if the ring is supposed to form on the α-atom, there are then 7 cases of agreement with the hypothesis of parallelism, 8 disagreements, and 9 remaining doubtful. If the ring forms on the β-carbon, there are then 10 cases of agreement and 10 of disagreement and 4 in doubt. If the ring forms on the δ-carbon, there result 6 agreements, 12 disagreements, and 6 doubtful. But it has been seen that if the ring forms on the γ-carbon there are 24 agreements, no disagreements, and none in doubt. As the chances that an event which can happen in two equally probable ways will happen in exactly the same way 24 times out of 24 trials is only 1 in 17,000,000, it seems certain that the lactonic ring in these monobasic sugar lactones forms on the γ-carbon atom.

(The following is quoted from an article published seven years later.) [92]

Occasion is taken here to record several developments of this relation which have appeared since its publication in 1910. Anderson [93] has shown that the rotation (+19°) of *d*-glucuronic lactone,



agrees with it, likewise the rotation (−201°) of *l*-mannosaccharic lactone,



since both rings of the latter substance are to be considered as on the left of the structure. The lactones of α-hydroxymethyl *d*-lyxonic and α-hydroxymethyl *d*-arabonic acids that were mentioned by Anderson have been shown by later work [94] to be the well-known lactones of *d*-lyxonic and *d*-arabonic acids which were mentioned in my first article.

By the cyanhydrin synthesis, Philippe [95] has prepared from glucononose two glucodeconic acids and has found the specific rotations

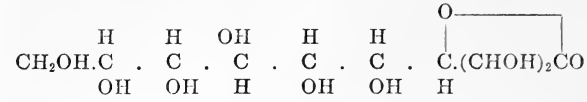
[92] Jour. Am. Chem. Soc., **39**, 462; 1917.

[93] Jour. Am. Chem. Soc., **34**, 51; 1912. Anderson shows in this article that the lactone rule holds for the lactones of the saccharinic acid group.

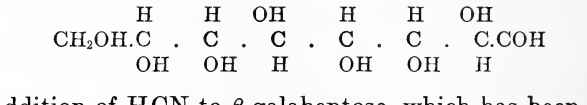
[94] Nef, Ann., **403**, 205; 1914.

[95] Ann. chim. phys., 8, **26**, 369; 1912.

of their lactones to be −35 and −40, respectively. The levorotation of these lactones indicates that the lactonic ring is on the left

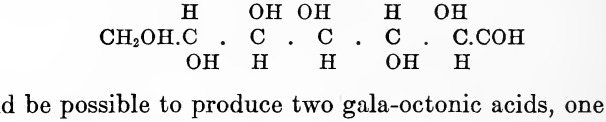


and while the configurations of the α- and β-carbons remain unknown, this determination of the position of the hydroxyl group on the γ-carbon shows the structure of *d*-gluco-octose, which has heretofore been undecided, to be

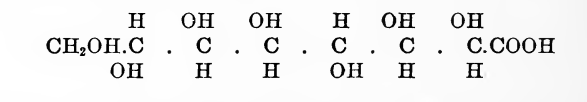


(1)

By the addition of HCN to β-galaheptose, which has been shown by Peirce[96] to be

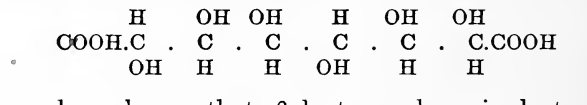


it should be possible to produce two gala-octonic acids, one of which would have the structure



(2)

The oxidation of (1) and (2) should give the same dibasic acid,



Anderson has shown that β-dextrosaccharonic lactone rotates slightly to the left (−4.7°) and is in disagreement, therefore, with the relation between rotation and structure because its γ-ring is to the right of the structure. As Anderson points out, however, β-saccharonic acid is strongly levorotatory, the specific rotation of its sodium salt being −35°, and the change of rotation due to lactone formation is in the direction called for by theory. The same explanation probably holds for the small levorotation of *d*-allonic lactone (−6.8°),[97] which is in the opposite direction to that indicated by theory. The direction of the rotation of the sirupy *d*-altronic lactone (+35), prepared by Levene and Jacobs, agrees with the theory. In doubtful cases where the lactone rotates only slightly, it would be well to consider the direction of the change in rotation due to lactone formation in applying the theory.

[96] J. Biol. Chem., **23**, 327; 1915.

[97] Levene and Jacobs, Ber., **43**, 3146; 1910.

Peirce's proof of the configuration of *d*-α-mannoheptose,

$$CH_2OH \cdot \begin{matrix} H \\ C \\ OH \end{matrix} \cdot \begin{matrix} H \\ C \\ OH \end{matrix} \cdot \begin{matrix} OH \\ C \\ H \end{matrix} \cdot \begin{matrix} OH \\ C \\ H \end{matrix} \cdot \begin{matrix} H \\ C \\ OH \end{matrix} \cdot CHO$$

shows that the lactone of *d*-manno-nononic acid, which Fischer and Passmore [98] prepared from this heptose by the cyanhydrin reaction through *d*-manno-octose, must have the configuration, in case it is a γ-lactone,

$$CH_2OH \cdot \begin{matrix} H \\ C \\ OH \end{matrix} \cdot \begin{matrix} H \\ C \\ OH \end{matrix} \cdot \begin{matrix} OH \\ C \\ H \end{matrix} \cdot \begin{matrix} OH \\ C \\ H \end{matrix} \cdot \begin{matrix} H \\ C.(CHOH)_2.CO \\ \text{—O———} \end{matrix}$$

This structure of the lactone would lead one to expect that the substance would rotate polarized light to the right, but Fischer and Passmore record a left-handed specific rotation, −41.0°. This large negative value is in complete opposition to the lactone rule; however, it should be taken into consideration that Fischer, in 1909,[99] mentioned that a repetition of the synthesis of higher carbon sugars from mannose had given different products from the first experiments, beyond the octose.

(e) THE STEREOCHEMICAL CONFIGURATIONS OF THE SUGARS FUCOSE AND RHODEOSE

The lactone rule of rotation was used in 1911 to obtain evidence on the configuration of the antipodal methyl pentose sugars fucose and rhodeose. It had been shown by Votoček and by Tollens that the observed production of *d*-trihydroxy glutaric acid from fucose and of *l*-trihydroxy glutaric acid from rhodeose limited the configuration of fucose to either

$$CH_3 \cdot CHOH \cdot \begin{matrix} H \\ C \\ OH \end{matrix} \cdot \begin{matrix} H \\ C \\ OH \end{matrix} \cdot \begin{matrix} OH \\ C \\ H \end{matrix} \cdot COH \qquad \text{(I)}$$

or

$$CH_3 \cdot CHOH \cdot \begin{matrix} H \\ C \\ OH \end{matrix} \cdot \begin{matrix} OH \\ C \\ H \end{matrix} \cdot \begin{matrix} OH \\ C \\ OH \end{matrix} \cdot COH \qquad \text{(II)}$$

and that of rhodeose to the mirror images of these structures. Votoček had selected for rhodeose the mirror image of structure (I), because of the fact that rhodeitol was found to resist oxidation by Bertrand's sorbose bacillus, an organism which had been found to oxidize only those alcohols of the sugar group in the structure of which the two carbons nearest the CH_2OH group have similarly placed hydroxyl groups. Tollens had selected structure (I) for fucose because the oxidation of the two fuco-hexonic acids resulting from fucose by the cyanhydrin synthesis to dibasic acids yielded no detectable amounts of mucic acid. It is apparent from the structures (I) and (II) that from (II) by these reactions mucic acid would be expected to result, while it should not be produced in case the structure is (I).

[98] Ber., 23, 2226; 1890.

[99] Untersuchungen über Kohlenhydrate und Fermente, p. 582.

The lactone rule of rotation was shown to furnish, in connection with the fact of the production of *d*- and *l*-trihydroxy glutaric acid from fucose and rhodeose, an independent proof of the configurations which agreed with the conclusions of Votoček and Tollens. The argument is as follows:[1]

Writing the carbon chain of rhodeose

$$\underset{}{CH_3.CHOH.C} \underset{(1)}{.} \underset{}{C} \underset{(2)}{.} \underset{}{C.COH} \quad \underset{(3)}{}$$

and referring to the fact that the rotation of rhodeonic lactone is $-76°$ [2] it will be seen that the lactonic ring from the end carbon to its γ-carbon is above the carbon chain and consequently the hydrogen atom in the sugar is below atom (1). The rotations of the rhodeohexonic lactones were found by Krauz [3] to be -35 and $-41°$, or, in other words, decidedly negative for both substances; consequently by similar reasoning the hydrogen atom in the sugar is to be chosen below carbon (2). The structure of rhodeose is thus determined partially to be

$$CH_3.CHOH.\overset{OH}{\underset{H}{C}} . \overset{OH}{\underset{H}{C}} . C.COH \qquad \text{(III)}$$

If the specific rotation of the heptonic lactones from fucose or rhodeose were known, the configuration of the groups attached to carbon (3) could be decided. In the absence of these values another way must be followed. From the fact that rhodeose yields *l*-trihydroxyglutaric acid on oxidation its structure must be either (I) or (II) (see preceding), and as only structure (I) has the hydrogen atoms below carbons (2) and (3), as required by (III), it must be selected for rhodeose. The structure of fucose is then the mirror image of (I).

It will be noticed that a configuration of the group $CH_3.CHOH$, which is an asymmetric one, is not indicated in I. The reason for this omission is that none of the facts which have been adduced to prove the structure of the other asymmetric groups has any bearing on the configuration of this one. Lately Tollens [4] has expressed the view that this group has the same structure in fucose that it has in *l*-galactose for the reason that the two sugars have nearly the same rotations, -75.5 and $-81°$. Votoček [5] does not consider this evidence of any weight. Regarding this question the following may be presented. The four sugars, fucose, *d*-arabinose, *l*-galactose and *l*-α-rhamnohexose have a large portion of their structure in common, as will be seen from the formulas, which are here printed in the γ-lactonyl ring form.

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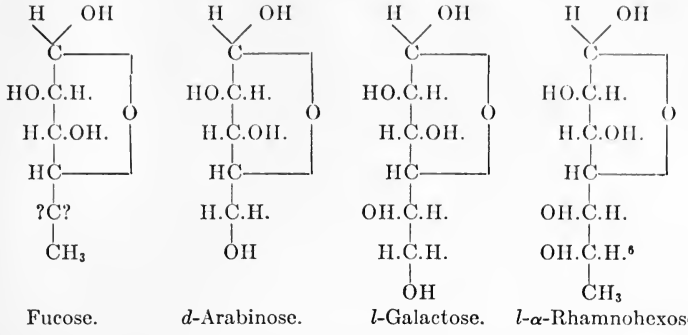
[1] Hudson, Jour. Am. Chem. Soc., **33**, 405; 1911.

[2] Votoček, Z. Zuckerind. Böh., **25**, 297; 1902. Müther and Tollens found the specific rotation of fuconic lactone to be $+71$ to $+78°$, which agrees with the accepted antipodal relation between fucose and rhodeose.

[3] Ber., **43**, 486; 1910.

[4] Ber., **40**, 2438; 1907; **42**, 2012; 1909.

[5] Ber., **43**, 469–475; 1910.



Fucose. *d*-Arabinose. *l*-Galactose. *l*-α-Rhamnohexose.

The portions of the structures included by the lactonyl rings are identical, but the portions below vary greatly, being in one case (*d*-arabinose) not even asymmetric. The specific rotations [7] of these sugars, or more correctly of the stable solutions which contain their α and β-forms in equilibrium, are, fucose −75.5°, *d*-arabinose −105°, *l*-galactose −81° and *l*-α-rhamnohexose −61°. These values are sufficiently alike, especially when they are reduced to the molecular rotations, to show that the common structure included within the lactonyl rings is the principal factor in fixing the rotation, and that the latter depends only in a minor degree upon the groups below the rings. This conclusion is emphasized by a peculiar relation between the rotations of these sugars and those of their lactones. Fuconic lactone rotates +75°, *d*-arabonic +74°, *l*-galactonic +78°, *l*-α-rhamnohexonic +84°,[8] or, in other words, the lactones have almost identical rotations, which are of opposite sign from those of the sugars. This evidence shows again that the rotations of these sugars and their lactones are principally due to their common element of structure which is within the lactonic ring, and that the configuration, weight, etc., of the groups which they do not possess in common have only a minor influence on the rotatory powers. Since such is the case it is hardly possible to agree with Tollens that the configuration of any of the groups below the ring can be decided from the rotations of the sugars. The only way at present known by which the configuration of the doubtful $CH_3.CHOH$ group of fucose and rhodeose can be determined is from a knowledge of the sign of the rotation of the methyl tetronic lactones which should be yielded by these sugars. This method has been used in determining the configuration of the similar group in the related methyl pentose, rhamnose, but the methyl tetronic lactones from fucose and rhodeose have not yet been

[6] The configuration of this group follows from the structure of rhamnose. See Jour. Am. Chem. Soc., **31**, 345; 1910 (p. 286).

[7] Quoted from Lippmann's "Chemie der Zuckerarten."

[8] For references see Jour. Am. Chem. Soc., **31**, 338-346; 1910.

prepared, and the difficulty of obtaining these rare sugars in quantity prevents me from attempting the preparation of these substances.[9]

9. THE PHENYLHYDRAZIDE RULE OF ROTATION (LEVENE (1915), HUDSON (1916)) [10]

The typical reaction by which [the phenylhydrazides] are formed is

$$\underset{\text{(gluconic acid)}}{CH_2OH.(CHOH)_4.COOH} + \underset{\text{(phenylhydrazine)}}{NH_2.NH(C_6H_5)} = H_2O + \underset{\text{(gluconic phenylhydrazide)}}{CH_2OH.(CHOH)_4.C(=O).NH.NH(C_6H_5)}$$

Such phenylhydrazides as a rule crystallize very readily and are very useful derivatives for identifying the monobasic acids of the sugar group. They have generally been characterized by their melting points and solubilities, and it is indeed unfortunate, from the standpoint of the matters that are to be discussed in the present article, that in only three instances has the optical rotatory power in water of a phenylhydrazide been recorded by the discoverer of the substance. These exceptions are β-galaheptonic phenylhydrazide, which was found by Fischer [11] to rotate to the left, $-6.32°$, *d*-erythronic phenylhydrazide, which was found by Ruff [12] to rotate to the right, $+17.5°$, and β-mannoheptonic phenylhydrazide, which was found by Peirce [13] to rotate to the left, $-25.8°$. Probably the reason why the rotations of the phenylhydrazides have not been measured in as extensive a way as have those of the lactones is because many of the phenylhydrazides are of low solubility in all solvents. However, in a recent article by the late J. U. Nef [14] measurements are recorded for the specific rotations in water of the phenylhydrazides of *d*-erythronic ($+12.0°$), *d*-threonic ($-28.8°$), *d*-lyxonic ($-11.2°$), *d*-gluconic ($+12.0°$), *d*-gulonic ($+13.7°$), *d*-idonic ($-12.4°$) and *d*-galactonic ($+11.0°$) acids; a consideration of the rotations of these substances leads directly to a very simple generalization which bears promise of being quite useful in the development of the chemistry of the sugars.

Referring to the configuration of the four hexonic phenylhydrazides that were measured by Nef

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[9] E. P. Clark (J. Biol. Chem., **54**, 65 (1922)) subsequently carried out the experiments here suggested, prepared the methyl tetronic lactone from fucose and found it strongly levorotatory in water ($[\alpha]_D^{25} = -63.6$) from which it follows that the configuration of fucose is

$$CH_3 . \underset{H}{\overset{OH}{C}} . \underset{OH}{\overset{H}{C}} . \underset{OH}{\overset{H}{C}} . \underset{H}{\overset{OH}{C}} . COH$$

and that the sugar belongs in the *l*-series and is to be designated *l*-fucose. It is a reduced *l*-galactose, just as rhamnose is a reduced *l*-mannose.

[10] Quotation from Jour. Am. Chem. Soc., **39**, 462; 1916.

[11] Ann., **288**, 152; 1895.

[12] Ber., **32**, 3680; 1899.

[13] J. Biol. Chem., **23**, 327; 1915.

[14] Ann., **403**, 204; 1914. The values used are taken from pp. 249, 271, 273, 295, 296, 298, 303.

	$HN.NH(C_6H_5)$	$HN.NH(C_6H_5)$	$HN.NH(C_6H_5)$	$HN.NH(C_6H_5)$
	O:C	O:C	O:C	O:C
(α)	HCOH	HCOH	OHCH	HCOH
(β)	OHCH	HCOH	HCOH	OHCH
(γ)	HCOH	OHCH	OHCH	OHCH
(δ)	HCOH	HCOH	HCOH	HCOH
	CH_2OH	CH_2OH	CH_2OH	CH_2OH
	d-gluconic	*d*-gulonic	*d*-idonic	*d*-galactonic

it will be observed that each structure contains the four asymmetric carbon atoms α, β, γ, and δ. Let it be assumed that the principle of optical superposition holds among the members of this group, and that therefore the rotation due to the α-carbon atom is—α when the OH group is on the left, as in the idonic derivative, and $+\alpha$ when it is on the right, as in the other three structures. Similarly, let the values of the rotations of the other asymmetric carbon atoms be $\pm\beta$, $\pm\gamma$ and $\pm\delta$, respectively. Then the molecular rotations of the four phenylhydrazides, of molecular weight 286, may be written:

Phenylhydrazide	Molecular rotation
(1) *d*-Gluconic acid	$+\alpha-\beta+\gamma+\delta=(+\ 12)\ (286)=+34.3(10)^2$
(2) *d*-Gulonic acid	$+\alpha+\beta-\gamma+\delta=(+13.7)\ (286)=+39.2(10)^2$
(3) *d*-Idonic acid	$-\alpha+\beta-\gamma+\delta=(-12.4)\ (286)=-35.5(10)^2$
(4) *d*-Galactonic acid	$+\alpha-\beta-\gamma+\delta=(+11.0)\ (286)=+31.5(10)^2$

Solving these four equations gives the values

$$\alpha=+37.3(10)^2,\ \beta=+3.9(10)^2,\ \gamma=+1.4(10)^2,\ \delta=-0.6(10)^2.$$

It will be observed at once that the value of α, which is the rotation of the α-carbon atom, is so very much larger than the values of the rotations of the other three carbons, that its sign determines the direction of the rotation of the hexonic phenylhydrazides. This conclusion is emphasized by the rotations of the phenylhydrazides of gulonic and idonic acids, which differ only in the configuration of the α-carbon atom, its hydroxyl being on the right in the gulonic, and on the left in the idonic compound; for the former the specific rotation is to the right, $+13.7$, and for the latter nearly an equal amount to the left, -12.4, showing that the α-carbon atom is responsible for nearly all the rotation. The conclusion may be expressed in the converse form, namely, that the direction of rotation of the phenylhydrazide indicates the configuration of the hydroxyl on the α-carbon atom. If the phenylhydrazide rotates to the right, the hydroxyl on the α-carbon is on the right and vice versa.

If it should be that this simple relation holds throughout the sugar group, or even holds in most instances, it would be quite a useful aid in the determination of structure. Thus, for example, the cyanhydrin synthesis yields two heptonic acids (α and β) from galactose because the symmetric carbonyl carbon of the sugar becomes the asymmetric α-carbon of the heptonic acids. Since Fischer has found,

as mentioned, the specific rotation of β-galaheptonic phenylhydrazide to be toward the left, −6.32°, it is to be concluded that the OH group is on the left of the α-carbon, which indicates that the structure of the corresponding sugar, β-galaheptose, is

$$\begin{array}{cccccccccc} & & H & & OH & & OH & & H & & OH & \\ CH_2OH & . & C & . & C & . & C & . & C & . & C & . & COH \\ & & OH & & H & & H & & OH & & H & \end{array}$$

This is indeed the structure which Peirce has recently conclusively established for β-galaheptose by showing that the alcohol from the epimeric α-galaheptose is the antipode of that from α-mannoheptose.

Since the structure of β-mannoheptonic phenylhydrazide has been shown by Peirce to be

$$\begin{array}{cccccccccc} & & H & & H & & OH & & OH & & OH & & O & \\ CH_2OH.C & . & C & . & C & . & C & . & C & . & C-NH.NH(C_6H_5) \\ & & OH & & OH & & H & & H & & H & & \end{array}$$

it is to be expected that its rotation is to the left, a conclusion which is confirmed by Peirce's measurement, $[\alpha]_D^{27} = -25.8°$.

There remain Nef's measurements of the rotations of the phenylhydrazides of *d*-erythronic, *d*-threonic, and *d*-lyxonic acids, which have the configurations:

d-erythronic phenylhydrazide:

$$\begin{array}{cccccccc} & & H & & H & & O & \\ CH_2OH.C & . & C & . & C-NH.NH(C_6H_5), & [\alpha]_D^{20} = +12.0 \\ & & OH & & OH & & & \end{array}$$

d-threonic phenylhydrazide:

$$\begin{array}{cccccccc} & & H & & OH & & O & \\ CH_2OH.C & . & C & . & C-NH.NH(C_6H_5), & [\alpha]_D^{20} = -28.8 \\ & & OH & & H & & & \end{array}$$

d-lyxonic phenylhydrazide:

$$\begin{array}{cccccccc} & & H & & OH & & OH & O \\ CH_2OH.C & . & C & . & C & . & C.NH.NH(C_6H_5), & [\alpha]_D^{20} = -11.2 \\ & & OH & & H & & H & \end{array}$$

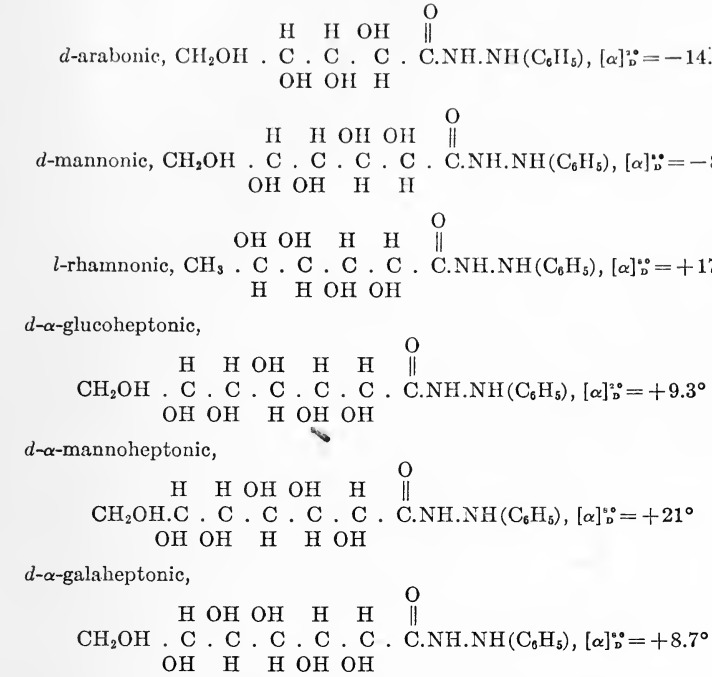
In the second and third of these the hydroxyl is on the left of the α-carbon and the rotation is to the left, while for *d*-erythronic phenylhydrazide the right-hand position of the hydroxyl corresponds with the observed right-hand rotation. Nef states that the specific rotation of pure *d*-talonic phenylhydrazide

$$\begin{array}{cccccccccc} & & H & OH & & OH & & OH & & O \\ CH_2OH.C & . & C & . & C & . & C & . & C-NH.NH(C_6H_5) \\ & & OH & H & & H & & H & & \end{array}$$

which he prepared in only a small quantity, was −25.1° in cold water. The direction of this rotation agrees with theory, but its value is larger than would be expected for a hexonic phenylhydrazide. All

of the recorded rotations of the phenylhydrazides, 10 in number, thus agree with the relation.

In order to test the matter further, I have prepared the following phenylhydrazides and measured their specific rotations in water:



A comparison of the position of the hydroxyl on the α-carbon with the direction of rotation of the phenylhydrazide shows that the rule holds for these 6 additional substances, making 16 phenylhydrazides upon which the correlation has been tested.

Recently Levene [15] has shown that the configuration of the α-carbon atom of the monobasic acids of the sugar group has a strong influence upon the rotation of the metallic salts of these acids, and that when the hydroxyl group on this carbon atom is to the right of the structure the salt is more dextrorotatory than is the salt of the epimeric acid which has its hydroxyl on the left of the α-carbon. Thus, for example, if the specific rotations of the sodium salts of *d*-gluconic (+11.78) and *d*-mannonic (−8.82) acids are compared, it is found that the acid which has the hydroxyl group on the right of its α-carbon, namely, gluconic acid, gives the more dextrorotatory salt. Levene has shown that this relation holds, in general, for epimeric pairs of such acids. It should be possible, as Levene indicates, to determine

[15] J. Biol. Chem., **23**, 146; 1915; also Levene and Meyer, Ibid., **26**, 355; 1916.

the configurations of many sugars by this relation, provided the necessary epimeric pairs of acids are prepared. It seems to me, however, that the phenylhydrazides offer a preferable way of determining these configurations because, as has been shown, it does not seem necessary to prepare the pair of epimeric acids since the direction of rotation of the phenylhydrazide of either one of them indicates the configuration of the α-carbon atom in both.[16] It is also usually the case that the phenylhydrazide is the most readily prepared crystalline derivative of the sugar acids. Levene and Meyer have measured the specific rotations of the sodium salts of all the hexonic acids, and there can be no question but that the measurements for the gluconate, mannonate, gulonate, and galactonate are closely correct, because these salts were prepared by neutralizing the very pure recrystallized lactones of these acids. It is interesting to calculate from their measurements the rotations of the four asymmetric carbon atoms in the configuration of the hexonic acids in order to compare them with the values that have been found for the phenylhydrazides. Since the sodium salts are largely dissociated while the phenylhydrazides are not, it is not surprising that the values derived from the salts are quite different from those found for the phenylhydrazides.

	Molecular configuration		Molecular rotation
Na *d*-gluconate	$+\alpha-\beta+\gamma+\delta=(+11.78)$	(218)	[17] $=+25.7(10)^2$
Na *d*-mannonate	$-\alpha-\beta+\gamma+\delta=(-\ 8.82)$	(218)	$=-19.2(10)^2$
Na *d*-gulonate	$+\alpha+\beta-\gamma+\delta=(+12.68)$	(218)	$=+27.6(10)^2$
Na *d*-galactonate	$+\alpha-\beta-\gamma+\delta=(+\ 0.40)$	(218)	$=+0.87(10)^2$

Solving these equations

$$\alpha=+22.4(10)^2,\ \beta=+13.4(10)^2,\ \gamma=+12.4(10)^2,\ \delta=+4.2(10)^2$$

Comparing these values with those recorded previously in this article for the asymmetric carbon atoms of the hexonic phenylhydrazides, it will be noted that the α-carbon in the salts has a larger influence upon the rotation than the β-, γ-, or δ-carbon but not a larger influence than the sum for these three atoms, which shows that the direction of rotation of the salt may be conditioned in certain configurations by the β-, γ-, and δ-carbons rather than by the α-carbon, which was not the case for the phenylhydrazides.

In concluding, it may be mentioned that the benzylphenyl hydrazones of the sugars exhibit an interesting correlation between structure and rotation. By inspection of the following table, it will be observed that the hydrazone rotates to the left when the asymmetric α-carbon atom of the configuration has its hydroxyl to the right and vice versa:

[16] Levene, in his 1915 article, had already pointed out that *d*-gluconic phenylhydrazide is more dextrorotary than *d*-mannonic phenylhydrazide, which indicated that the phenylhydrazides of such epimeric acids follow the same rule of rotation that Levene found for the salts. See also p. 298.

[17] Molecular weight of the sodium salt.

Benzylphenyl hydrazone	Position of OH on α-carbon	$[\alpha]_D^{20°}$	Solvent
d-Erythrose [1]	Right	−32	Alcohol.
Methyl tetrose [2]	do	−6.5	Do.
l-Arabinose [3]	do	−12.1	Methyl alcohol.
Rhamnose [3]	do	−6.4	Do.
d-Glucose [3]	do	−33	Do.
d-Gulose [4]	do	−24	Do.
d-Galactose [3]	do	−17.2	Do.
l-Erythrose [5]	Left	+32.8	Alcohol.
d-Lyxose [6]	do	+26.4	Do.
Fucose [7]	do	+9.1	Pyridine.
d-Mannose [3]	do	+29.8	Methyl alcohol.

[1] Ruff, Ber., **32**, 3672; 1899.
[2] Ruff and Kohn, Ber., **35**, 2362; 1902.
[3] Lobry de Bruyn and Van Ekenstein, Rec. trav. chim. Pays Bas, **15**, 226; 1896.
[4] Lobry de Bruyn and Van Ekenstein, Rec. trav. chim. Pays Bas, **19**, 182; 1900.
[5] Ruff, Ber., **34**, 1366; 1901.
[6] Ruff and Ollendorff, Ber., **33**, 1801; 1900.
[7] Tollens and Müther, Ber., **37**, 307; 1904.

The benzylphenyl hydrazones exhibit mutarotation and doubtless exist, therefore, in solution in isomeric forms and the rotations of their solutions refer to mixtures of such forms in equilibrium. Their structures are not as simple and as definitely known as are those of the acid phenylhydrazides, the rotations have not been measured in one solvent throughout, and the correlation between their structure and rotation is not proved in as many cases as have been shown for the phenylhydrazides. Nevertheless, the existing data indicate that such a relationship probably holds.

10. THE AMIDE RULE OF ROTATION [18]

Weerman [19] has recently published measurements of the rotatory powers in water of the amides of seven monobasic acids of the sugar group. A comparison of the configurations that have been established for these acids or their amides by Fischer with their rotations is shown in the following table:

TABLE 16.—*Configurations and specific rotations*

Amide	Fischer's configuration	α-carbon OH position	Specific rotation
d-Gluconic amide	$CH_2OH \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CNH_2$	Below	+33.8°
d-Galactonic amide	$CH_2OH \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CNH_2$	do	+36.7°
l-Mannonic amide	$CH_2OH \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CNH_2$	do	+29.9°
d-Gulonic amide	$CH_2OH \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CNH_2$	do	+16.1°
l-Arabonic amide	$CH_2OH \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CNH_2$	do	+38.4°
l-Ribonic amide	$CH_2OH \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot CNH_2$	Above	−15.7°
d-Xylonic amide	$CH_2OH \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CNH_2$	Below	+44.5°

[18] Quotation from Hudson, Jour. Am. Chem. Soc., **39**, 465; 1917.
[19] Dissertation "Over de Inwerking van Natriumhypochloriet op Amiden van Onverzadigde Zuren en Oxyzuren," published by A. H. Kruyt, Amsterdam, 1916.

It will be seen that the dextrorotary amides have the hydroxyl group below the asymmetric α-carbon atom, while the levorotary ones have it above. Recently Dr. E. Yanovsky has measured for me the rotation of *d*-α-glucoheptonic amide,

$$\begin{array}{cccccccccc} & & H & & H & & OH & H & H & O \\ CH_2OH & . & C & . & C & . & C & . & C & . & CNH_2, \\ & & OH & & OH & & H & & OH & OH & \end{array}$$

and Dr. L. H. Chernoff that of *l*-rhamnonic amide,

$$\begin{array}{ccccccccc} & OH & OH & H & & H & O \\ CH_3 . & C & . & C & . & C & . & CNH_2. \\ & H & & H & & OH & OH & \end{array}$$

Both substances were dextrorotary in agreement with the above relation. This relation is the same one that has been noted previously by Levene [20] for the direction of rotation of the salts and the phenylhydrazides of such acids. It is analogous to the relation that I have shown to hold between the direction of rotation and the position of the hydroxyl group on the γ-carbon atom of the lactones of these acids.[21] These rules for the direction of rotation may be easily remembered if the formulas are looked upon as placed vertically with the carboxyl group at the top, since a hydroxyl group on the right of the γ-carbon atom indicates that the lactone will rotate to the right and vice versa, and a hydroxyl on the right of the α-carbon indicates that the amide and the phenylhydrazide will rotate to the right. It is not surprising that the rotations of the amides are found to follow the same rule as do those of the phenylhydrazides because the latter compounds may be looked upon as substituted amides, $R.CHOH.CONH_2$ becoming $R.CHOH.CONH.NH(C_6H_5)$. Probably other substituted amides of these acids, such as the anilides $R\text{-}CHOH.CONH.C_6H_5$, follow the same rule.

It would be interesting to consider in a quantitative way the rotations of the amides that are mentioned in the table, but Weerman's actual readings are so small, in most cases less than two degrees, that the recorded specific rotations may be uncertain to the extent of several per cent. It seems possible, however, to draw at least one quantitative conclusion from them. By the same method of calculation that was used for the phenylhydrazides [22] the individual specific rotations of the 4 asymmetric carbon atoms of the hexonic amides may be found from the rotations of gluconic, mannonic, gulonic, and galactonic amides to be, for the α-carbon $+32$, β-carbon -10, γ-carbon -1, and the δ-carbon -7. Although these values may be changed somewhat by more accurate measurements they clearly show that the α-carbon is so strongly rotatory in these compounds that its influence determines the direction of rotation for the whole structure.

[20] J. Biol. Chem., **23**, 145; 1915; Levene and Meyer, Ibid., **26**, 355; 1916; **31**, 623; 1917. Regarding the phenylhydrazides, see also Hudson, Jour. Am. Chem. Soc., **39**, 462; 1917 (p. 292).

[21] Jour. Am. Chem. Soc., **31**, 338; 1910 (p. 280).

[22] Jour. Am. Chem. Soc., **39**, 465; 1917 (p. 293).

(a) THE ROTATORY POWERS OF TARTARIC AND TARTRAMINIC ACIDS AND TARTRAMIDE

It has been shown by Fischer [23] that dextrorotary tartaric acid ($[\alpha]_D^{20} = +14°$ in 5 per cent aqueous solution [24]) has the configuration

$$\begin{array}{ccccccc} & & \mathrm{OH} & & \mathrm{H} & & \\ \mathrm{COOH} & . & \mathrm{C} & . & \mathrm{C} & . & \mathrm{COOH} \\ & & \mathrm{H} & & \mathrm{OH} & & \end{array}$$

hence its mono-amide, tartraminic acid, must have the configuration

$$\begin{array}{ccccccc} & & \mathrm{OH} & & \mathrm{H} & & \\ \mathrm{CONH_2} & . & \mathrm{C} & . & \mathrm{C} & . & \mathrm{COOH} \\ & & \mathrm{H} & & \mathrm{OH} & & \end{array}$$

and its di-amide, tartramide, the structure

$$\begin{array}{ccccccc} & & \mathrm{OH} & & \mathrm{H} & & \\ \mathrm{CONH_2} & . & \mathrm{C} & . & \mathrm{C} & . & \mathrm{CONH_2}. \\ & & \mathrm{H} & & \mathrm{OH} & & \end{array}$$

In the last formula the position of the hydroxyl group on each of the two α-carbons is to be considered as on the right, the carbon chain being written vertically and the two amide groups placed successively at the top. Both asymmetric carbon atoms, therefore, rotate to the right and it is to be expected that tartramide has a high dextrorotation; in agreement with this conclusion its specific rotation in water has been found by Frankland and Slator [25] to be $+106.5$. Walden [26] found the value 109°. Since the configuration of tartraminic acid may be regarded as consisting of half that of tartramide and half that of tartaric acid, the rotation of tartraminic acid may be expected to be the mean of $+14$ and $+106.5$ or $+60°$. In satisfactory agreement with this calculation Weerman [27] has found the value $+64$, and the last unit is uncertain because the actual reading that he observed was only about 4°. If Walden's value of 109 is used in the calculation, the agreement is still better. Both tartramide and tartraminic acid, therefore, conform to the general relation for the direction of rotation of the amides.

(b) THE CONFIGURATIONS OF THE ACTIVE MALIC ACIDS

Naturally occurring malic acid is of levorotation in dilute aqueous solution. Its antipode has been produced by the reduction of natural (dextrorotary) tartaric acid [28] with hydriodic acid; hence Fischer has assigned to levorotatory malic acid the configuration

$$\begin{array}{ccccc} & & \mathrm{OH} & & \\ \mathrm{COOH.CH_2} & . & \mathrm{C} & . & \mathrm{COOH}. \\ & & \mathrm{H} & & \end{array}$$

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[23] Ber., **29**, 1377; 1896.

[24] Landolt, Ber., **6**, 1073; 1873.

[25] J. Chem. Soc., **83**, 1354; 1903. Regarding the dextrorotation of a large number of substituted di-amides, of dextro tartaric acid, which agree with the relation, see Frankland and Twiss, J. Chem. Soc., **89**, 1853; 1906.

[26] Z. physik. Chem., **17**, 707; 1895.

[27] Dissertation, p. 109.

[28] Bremer, Ber., **8**, 861; 1875.

The di-amide of this acid must accordingly be assigned the configuration

$$CONH_2.CH_2 \cdot \overset{OH}{\underset{H}{C}} \cdot CONH_2.$$

Since this formula contains only one asymmetric carbon atom and the hydroxyl group is on the left of this carbon, it is to be expected that the di-amide of natural malic acid will be levorotary in case the above configuration is correct. Such is the fact, the specific rotation in water having been observed by Walden [29] to be $-38°$. This agreement is supported by Walden's further observation that the di-anilide, di-*o*-toluide, and di-*p*-toluide of natural malic acid are all strongly levorotary substances. A number of other substituted malamides that have been measured by Frankland and his pupils [30] also agree with the relation. This confirmation of the configuration of the active malic acids is of theoretical value just now because Freudenberg [31] has recently passed from active malic to active lactic and active glyceric acids, and has obtained the configurations of the latter two in terms of the configuration of malic acid. As Freudenberg remarks, however, the yield of active malic acid from the reduction of dextrorotary tartaric acid is only 2 per cent which, of course, is so low that the selected configuration of malic acid is rendered doubtful. The present new proof, however, shows that the hitherto accepted configuration of Fischer's is correct and that the configurations which Freudenberg has assigned to lactic and glyceric acids are in consequence also correct. The configurations of active lactic, glyceric, and α-hydroxy butyric acids could doubtless be obtained directly, without reference to syntheses from other substances if the rotations of the corresponding amides were known, which is not the case at present.[32]

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[29] Z. physik. Chem., **17**, 249; 1895.

[30] McCrae, J. Chem. Soc., **83**, 1324; 1903.

[31] Ber., **47**, 2027; 1914.

[32] After sending in this article for publication I have fortunately found that Frankland, Wharton, and Aston (J. Chem. Soc., **79**, 266; 1901) have measured the rotation of the amide of one of the active forms of glyceric acid. Their acid rotated to the right, its calcium salt rotated to the left, and its amide rotated strongly to the left ($[\alpha]_D^{5°} = -46°$ for the liquid amide without any solvent and $[\alpha]_D^{5°} = -66°$ in methyl alcohol). There can hardly be any doubt that the amide would rotate to the left in water. Consequently dextrorotary glyceric acid is to be assigned the configuration

$$\begin{array}{l} COOH \\ \cdot \\ HOCH \\ \cdot \\ CH_2OH \end{array}$$

This confirms Freudenberg's proof for glyceric acid.

(c) THE CONFIGURATIONS OF THE ACTIVE MANDELIC ACIDS [33]

The mandelic acid which is obtained from amygdalin has a specific rotation [34] to the left, $[\alpha]^{2.2}_{D} = -153°$ in water and $-148°$ in acetone. Its amide has been found by Walden to rotate to the left, $[\alpha]^{2.2}_{D} = -67$ in acetone and without doubt it would be strongly levorotary in water. The configurations of the active mandelic acids are accordingly considered to be

COOH	COOH
HCOH	OHCH
C_6H_5	C_6H_5
Dextro-mandelic acid.	Levo-mandelic acid.
$[\alpha]^{25}_{D} = +153.$	$[\alpha]^{25}_{D} = -153.$

(d) THE ROTATORY POWERS OF THE AMIDES OF SEVERAL ALPHA-HYDROXY ACIDS OF THE SUGAR GROUP [35]

In a recent article [36] it was shown that Weerman's measurements of the rotatory powers of the amides of 7 α-hydroxy acids of the sugar group lead to the generalization that the α-carbon atom is principally responsible for the rotation of these substances and that when the hydroxyl group is on the right of this carbon atom, in the configurations of Fischer's, the amide rotates to the right and vice versa. This conclusion was borne out further by the known configurations and rotations of tartraminic acid, tartramide and the amides of malic and glyceric acids. By its application to the amide of mandelic acid the configurations of the active forms of this acid were placed in the system that Fischer originated for the sugar group, which will doubtless in time grow to include most optically active substances. In that article it was stated that Weerman's measurements seemed to lack the precision that would be required in a quantitative study of the rotations of the other active carbon atoms of the amides of the sugar acids. At present we wish to treat this subject quantitatively, basing the study upon measurements that one of us (S. K.) has made during the past year. These measurements confirm the generalization already mentioned, but they differ in some instances from Weerman's data and lead to some interesting conclusions that are not apparent from his measurements.

Consider first the molecular rotations (m. w. 195) in aqueous solution of the amides of the group of acids that are related to the hexoses, the so-called hexonic acids, namely, gluconic, mannonic, gulonic, and galactonic acids.

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[33] [Attention is directed to the subsequent correction of an error in reasoning that occurs in this paragraph, which Freudenberg has noticed. See Jour. Am. Chem. Soc., **46**, 484; 1924 (p. 330.]

[34] Walden, Z. physik. Chem., **17**, 706; 1895.

[35] Hudson and Komatsu, Jour. Am. Chem. Soc., **41**, 1141; 1919.

[36] Jour. Am. Chem. Soc., **40**, 813; 1918.

TABLE 17.—*Configurations and rotations of hexonic amides*

Amide	Fischer's configuration	Specific rotation	Molecular rotation
d-Gluconic amide	$CH_2OH.\overset{OH}{C}.\overset{OH}{C}.\overset{H}{C}.\overset{OH}{C}.CNH_2$	+31.2	$+60.8(10)^2$
d-Mannonic amide	$CH_2OH.\overset{OH}{C}.\overset{OH}{C}.\overset{H}{C}.\overset{H}{C}.CNH_2$	−17.3	$-33.7(10)^2$
d-Gulonic amide	$CH_2OH.\overset{OH}{C}.\overset{H}{C}.\overset{OH}{C}.\overset{OH}{C}.CNH_2$	+15.2	$+29.6(10)^2$
d-Galactonic amide	$CH_2OH.\overset{OH}{C}.\overset{H}{C}.\overset{H}{C}.\overset{OH}{C}.CNH_2$	+30.2	$+58.9(10)^2$

Since there are four asymmetric carbon atoms in these structures the rotation of each of them can be calculated from the rotations of the four amides on the assumption of the principle of optical superposition. The details of the method of calculation have already been published.[37] It is found in this way that the molecular rotations for the four carbon atoms, calling the active atom next the amide end the α-carbon, have the following values when the hydroxyl group is on the lower side of its carbon atom (or is on its right when the formula is written vertically with the amide group at the top): α-carbon $= +47.25(10)^2$, β-carbon $= -14.65(10)^2$, γ-carbon $= +0.95(10)^2$, and δ-carbon $= -2.05(10)^2$. It will be noticed that the numerical values decrease as the carbon atom is further removed from the amide end (the difference between the values for the γ- and δ- atoms, both of which are very small, are probably near the limit of accuracy of the data). The alternation in the sign of the rotation of the successive carbon atoms is also noteworthy, suggesting the alternation in positive and negative affinity that is often ascribed to the carbons in a chain.

Consider next the amides of several of the acids of the heptose group.

TABLE 18.—*Configurations and rotations of heptonic amides*

Amide	Fischer's configuration	Specific rotation	Molecular rotation (mol. wt. 225)
α-Glucoheptonic	$CH_2OH.\overset{OH}{C}.\overset{OH}{C}.\overset{H}{C}.\overset{OH}{C}.\overset{OH}{C}.CNH_2$	+10.6	$+23.8(10)^2$
β-Glucoheptonic	$CH_2OH.\overset{OH}{C}.\overset{OH}{C}.\overset{H}{C}.\overset{OH}{C}.\overset{H}{C}.CNH_2$	−30.2	$-67.9(10)^2$
α-Mannoheptonic [a]	$CH_2OH.\overset{OH}{C}.\overset{OH}{C}.\overset{H}{C}.\overset{H}{C}.\overset{OH}{C}.CNH_2$	+28.0	$+63.0(10)^2$
α-Galaheptonic	$CH_2OH.\overset{OH}{C}.\overset{H}{C}.\overset{H}{C}.\overset{OH}{C}.\overset{OH}{C}.CNH_2$	+14.3	$+32.2(10)^2$

[a] Hudson and Monroe, Jour. Am. Chem. Soc., **41**, 1140; 1919.

[37] Jour. Am. Chem. Soc., 39, 465; 1917.

Although it is not possible to calculate the rotations of all five of the active carbon atoms in these chains, because only four observations are at hand, nevertheless the following molecular rotations may be determined: α-carbon $= +45.85(10)^2$, β-carbon $= -19.6(10)^2$, δ-carbon $= -4.2(10)^2$, ϵ-carbon $-\gamma$-carbon $= +1.75(10)^2$. It is noticeable again that the sign alternates from carbon to carbon. The numerical value for the α-carbon is almost the same as was found for the hexonic amides, showing that the principle of optical superposition holds at least closely in passing from one of these groups to the other. Also the values for the other carbons correspond very well within the two groups. It seems highly probable, therefore, that the principle holds closely among the members of each group. One could, of course, calculate with fair approximation the rotation of the amides of several of the hexonic and heptonic acid amides that have not yet been measured, such as allonic amide or gulo-heptonic amide, but the mention of this may suffice at present.

Consider next the amides of the pentonic acids.

TABLE 19.—*Configurations and rotations of pentonic amides*

Amide	Fischer's configuration	Specific rotation	Molecular rotation (mol. wt. 165)
l-Arabonic amide	$CH_2OH.\overset{OH}{\underset{H}{C}}.\overset{OH}{\underset{H}{C}}.\overset{H}{\underset{OH}{C}}.CONH_2$	+37.5	$+61.9(10)^2$
l-Ribonic amide	$CH_2OH.\overset{OH}{\underset{H}{C}}.\overset{OH}{\underset{H}{C}}.\overset{OH}{\underset{H}{C}}.CONH_2$	−16.4	$-27.1(10)^2$
d-Xylonic amide	$CH_2OH.\overset{H}{\underset{OH}{C}}.\overset{OH}{\underset{H}{C}}.\overset{H}{\underset{OH}{C}}.CONH_2$	+44.5	$+73.4(10)^2$

From these three values the molecular rotations of the three active carbon atoms in the pentonic amides may be calculated to be, α-carbon $= +44.5(10)^2$, β-carbon $= -23.15(10)^2$, γ-carbon $= +5.75(10)^2$. The value for *d*-xylonic amide is taken from Weerman's article, as we have not been able to crystallize this substance. The value for the α-carbon is obtained by the use only of our own data for the amides of arabonic and ribonic acids, both of which have been prepared in very pure crystalline condition. A change in the value for the amide of xylonic acid would not affect the value of the rotation of the α-carbon atom but would alter those of the β- and γ-carbons. The alternation in sign of the successive carbon atoms is again apparent, and likewise the decrease in the rotation as the carbon atom is further removed from the amide end. The numerical value for the α-carbon, $44.5(10)^2$, is quite near those that have been found for this carbon in the hexonic and heptonic acids, showing that the principle of optical superposition holds fairly closely for these amides.

Lastly, mention is made of the diamides of three of the dibasic acids of the sugar group, *d*-mannosaccharic and *d*-saccharic acids and tartaric acid.

TABLE 20.—*Configurations and rotations of three diamides*

Diamide	Fischer's configuration	Specific rotation	Molecular rotation
d-Saccharic diamide	$NH_2C(O).CH(OH).CH(OH).CH(OH).CH(H).CONH_2$	+13.3	$+27.7(10)^2$
d-Mannosaccharic diamide.	$NH_2C(O).CH(OH).CH(OH).CH(H).CH(H).CONH_2$	−24.4	$-50.8(10)^2$
Tartaric diamide	$NH_2C(O).CH(H).CH(OH).CONH_2$	[1] +106.5	$+157.6(10)^2$

[1] Measurement by Frankland and Slator, J. Chem. Soc., **83**, 1354; 1903.

If the active carbon atoms in these structures be named in the manner that has been followed for the monoamides, one must name from each end toward the center and in giving a sign to the rotations of the carbons of the left half must consider the structure to be turned through 180° in the plane of the paper, so as to put the left-hand amide group around to the right end. Thus the four asymmetric carbons in *d*-saccharic diamide would be given the following signs and designations:

$$NH_2OC.\underset{-\alpha}{CH(OH)}.\underset{-\beta}{CH(OH)}.\underset{-\beta}{CH(H)}.\underset{+\alpha}{CH(OH)}.CONH_2.$$

Two equations may now be set up for the molecular rotations of the diamides of *d*-saccharic and *d*-mannosaccharic acids, respectively.

$$d\text{-Saccharic diamide} -\alpha-\beta-\beta+\alpha=+27.7(10)^2$$
$$d\text{-Mannosaccharic diamide} -\alpha-\beta-\beta-\alpha=-50.8(10)^2$$

Solving these two equations for the two unknown quantities gives $\alpha=+39.25(10)^2$ and $\beta=-13.85(10)^2$.

In the case of tartramide there are two α-carbons, both to be considered positive, and no β-carbons, hence $2\alpha=+157.6(10)^2$ and $\alpha=+78.8(10)^2$.

The values for the carbons of the hexaric diamides are near those for the hexonic monoamides and are of the same sign. In the case of the tartaric diamide the sign is the same for the α-carbon, but its numerical value is much larger, possibly because the two α-carbons, of strong rotation, are not separated in this structure by any intervening carbon atoms.

It would be desirable to extend this study to the amides of other optically active dibasic acids. The present data are sufficient to allow the calculation of the rotatory powers of the diamides of all the hexaric acids.

TABLE 21.—*Molecular rotations of the active carbon atoms of amides from the sugar group*

Carbon	4-carbon series, diamide	Pentonic amides	Hexonic amides	Heptonic amides	Hexaric diamides
α[1]	$+78.8(10)^2$	$+44.5\ (10)^2$	$+47.25(10)^2$	$+45.85(10)^2$	$+39.25(10)^2$
β		$-23.15(10)^2$	$-14.65(10)^2$	$-19.6\ (10)^2$	$-13.85(10)^2$
γ		$+5.75(10)^2$	$+0.95(10)^2$	(?)	
δ			$-2.05(10)^2$	$-4.2\ (10)^2$	
ϵ				(?)	

[1] With the formula of the compound written vertically and the amide group placed at the top, if the OH group of the particular carbon atom is on the right of the structure the sign of rotation of the carbon is that given in the table.

In Table 21 are recorded the values that have been adduced for the molecular rotations of the different carbon atoms in these various amides. The values for the β- and γ-carbons of the pentonic amides depend upon Weerman's value for xylonic amide. We suspect that his value is slightly too high. If the rotation of the γ-carbon may be neglected in the pentonic amides, as seems probable from its low values in the hexonic series, the value of the rotation of the β-carbon can be calculated without using Weerman's determination. It is found to be $-17.4(10)^2$, which is near the average of the values that have been found in the hexonic and heptaric series. Using this value and neglecting that of the γ-carbon, gives for xylonic amide the rotation of arabonic amide, $+37.5°$, in place of Weerman's measurement, $+44.5°$.

(e) THE LACTONE AND THE AMIDE OF METHYL TETRONIC ACID [38]

Methyltetronic acid has been previously prepared by Ruff and Kohn,[39] who obtained it in the form of its lactone through the oxidation of methyltetrose with bromine. Methyltetrose, however, is difficult to make. We have obtained this lactone very easily by a simple method recently described by Nef, Hedenburg, and Glattfeld [40] for the oxidation of arabinose and xylose. By passing a current of air through dilute solutions of these pentoses, they obtained *l*-erythronic lactone from *l*-arabinose and *d*-threonic lactone from *d*-xylose. Applying this method to rhamnose, one would expect that its oxidation should yield methyltetronic lactone, and this proves to be the fact. Our yield of lactone was 9.6 per cent of the theoretical. This is considerably more than Ruff and Kohn obtained (2 per cent), and as the method which we have followed is much more direct and simple than theirs it is recommended for the preparation of this lactone.

[38] Quotation from Hudson and Chernoff, Jour. Am. Chem. Soc., **40**, 1005; 1918.
[39] Ber., **35**, 2365; 1902.
[40] Jour. Am. Chem. Soc., **39**, 1638; 1917.

The configuration of rhamnose has been established [41] to be that of a methylpentose,

$$\begin{array}{cccccc} & OH & OH & H & H & \\ CH_3.C & . & C & . & C & . & C & . & CHO \\ & H & H & & OH & OH & \end{array}$$

hence the configuration of methyltetronic lactone (considered to be a γ-lactone) is

$$\begin{array}{ccccccc} & & \multicolumn{3}{c}{\overset{\displaystyle O}{\overbrace{\qquad\qquad}}} & \\ & & | & & & | & \\ & & OH & & H & & \\ CH_3.C & . & C & . & C & . & CO \\ H & & H & & OH & & \end{array}$$

By passing dry ammonia gas into a solution of this lactone in ether we have prepared the crystalline amide of methyltetronic acid, the structure of which must be

$$\begin{array}{cccccc} & OH & OH & H & & \\ CH_3.C & . & C & . & C & . & CONH_2 \\ & H & H & & OH & & \end{array}$$

Since the hydroxyl group is on the right of the asymmetric α-carbon atom of the amide it is to be expected [42] that the amide will be dextrorotary. This proves to be the case, its rotation in water being strongly to the right.

(1) Methyltetronic Acid Lactone.—Fifty g of crystalline rhamnose monohydrate was dissolved in 250 cc of hot water and the solution was made up to 5,250 cc. To this was added a solution of 93.5 g of pure potassium hydroxide in 250 cc of water. Air freed from carbon dioxide by passing over sodium hydroxide was then drawn through the mixture continuously for three days by the suction of a water pump. The diameter of the air inlet tube was 5 mm. The rate of flow was approximately 1.5 liters per minute. If the air is not admitted fast enough the solution will turn yellow, the color disappearing after several hours if the rate is increased. During daytime the solution was heated to 40 to 50°. At the end of the reaction the solution was colorless. Conc. hydrochloric acid was then added, the final addition being made with 10 per cent acid using congo red paper as an indicator. The paper is pink in alkaline solution, takes on a light purple color when the organic sugar acids are liberated from their salts, and becomes dark blue fairly sharply when free hydrochloric acid is present. Acid was added just until the color became fairly blue, showing that the organic acids were entirely liberated from their salts, but very little or no hydrochloric was present in the free state. The solution was then evaporated to dryness in vacuo. The distillate showed the presence of formic acid

[41] Fischer and Morrell, Ber., **27**, 382; 1894; Fischer and Zach, Ber., **45**, 3761; 1912; Hudson, Jour. Am. Chem. Soc., **31**, 345; 1910.

[42] Hudson, Jour. Am. Chem. Soc., **40**, 813; 1918.

by reducing Fehling's solution. The white crystalline residue, somewhat gummy, was then boiled with absolute alcohol several times and filtered. The combined alcoholic solutions were then evaporated in vacuo to a thick red residue which was almost entirely soluble in ethyl acetate. This solution was filtered from the crystalline residue of potassium chloride. The ethyl acetate solution was evaporated on the steam bath, and the residue was triturated with warm ether until no more color dissolved. About 3 g of a white crystalline substance was obtained from this ether extract by evaporating it almost to a sirup and letting stand several days. The residue that was insoluble in ether yielded about half a gram more of crystals of the same substance on standing in the open air several days.

The crystals melted at 121° and on recrystallization from absolute alcoho yielded 2 g of needle-like crystals melting at 123°. A solution containing 0.3187 g substance made up to 25 cc with water rotated −1.14 circular degrees to the left in a 2 dcm tube, hence $[\alpha]_D = -44.7°$. Methyltetronic acid lactone that was obtained by Ruff and Kohn from the oxidation of methyltetrose with bromine melted at 121° and had a specific rotation of −47.5°.

The crystals of this lactone are easily soluble in cold absolute ether, contrary to the behavior of most lactones of the sugar group. Ruff and Kohn describe the crystals as rather difficultly soluble in benzene, ether or chloroform and very soluble in alcohol or ethyl acetate. We have verified these statements except with reference to ether, which dissolves the crystals readily.

(2) Methyltetronic Acid Amide.—One g of methyltetronic acid lactone was dissolved in 30 cc of cold ether and dry ammonia gas was passed through the solution for 20 minutes. An amorphous white precipitate settled out on the bottom of the flask. By rubbing it under ether with a glass rod for several minutes it became crystalline and could easily be filtered by suction. The yield was nearly quantitative. The substance was recrystallized from absolute alcohol, in which it was very soluble. The crystals were large plates which melted with decomposition at 135°.

A solution of 0.5404 g substance made up to 25 cc with water, using a 4 dcm tube, showed a dextrorotation of 4.74 circular degrees; hence $[\alpha]_D = +54.8°$. Nitrogen was determined by the Kjeldahl method.

Calc. for $C_5H_{11}O_4N$: N, 9.40. Found: 9.30.

In analogous manner E. P. Clark [43] has subsequently prepared the lactone of a methyltetronic acid resulting from the oxidation of fucose (methyl fuco-tetronic lactone, see p. 292) and from it methyl fuco-tetronic amide, the dextrorotation of which ($[\alpha]_D^{20} = +18.5$ in water) agrees with the amide rule, since its configuration is

$$\begin{array}{ccccccc} OH & & H & & H & & \\ CH_3.C & . & C & . & C & . & CONH_2 \\ H & & OH & & OH & & \end{array}$$

[43] Jour. Biol. Chem., **54**, 65; 1922.

He has likewise prepared fuconic amide and has found its rotation ($[\alpha]_D^{20} = -31.1$ in water) to agree with the amide rule (see p. 292 for the configuration of fucose).

(f) THE AMIDE OF α-MANNOHEPTONIC ACID [44]

It was first noted by Fischer [45] as a precipitate settling from the reaction mixture of hydrogen cyanide and *d*-mannose in aqueous solution. He identified the substance as an amide by its behavior toward alkalies and iron salts, found its m. p. to be 182 to 183°, but published no analysis or record of its purification. Its specific rotation was not measured. As we desired to know its rotatory power, we prepared it in similar manner, but soon reached the conclusion that it was by no means a pure compound because on successive recrystallizations its m. p. rose to 193 to 194° and its specific rotation increased from +4 to +28°. These higher values were found only after the substance had been recrystallized six times, but further recrystallization did not change them. As the substance was difficult to purify and there seemed a possibility of the presence in it of the isomeric β-*d*-mannoheptonic amide, or some other impurity, a second method for preparing it was studied. Ten g of pure crystalline α-*d*-mannoheptonic lactone was dissolved in 100 cc of 50 per cent alcohol, the solution was cooled with ice and ammonia was passed into it to saturation. A fine, white, granular precipitate formed, which was filtered off and washed with cold 50 per cent alcohol. Its m. p. was 184 to 185° and $[\alpha]_D^{20} = +14$. After only two recrystallizations from hot water its m. p. was 193 to 194° and $[\alpha]_D^{20} = +27.8°$, both of which agree with the values found for the other preparation of this amide.

The purified amide from the hydrogen cyanide reaction was found to contain 6.1 and 5.9 per cent nitrogen in two analyses by the Kjeldahl method, which agree with the theoretical value for $CH_2OH.CHOH.CHOH.CHOH.CHOH.CHOH.CONH_2$, 6.2 per cent. The purified amide made by the action of ammonia on the lactone gave 5.9 and 6.1 per cent nitrogen. An aqueous solution of the purified amide from the HCN reaction, containing 0.542 g substance in 50 cc solution rotated 1.21° to the right at 20° in a 4 dcm tube with sodium light; hence $[\alpha]_D^{20} = +28.0$. A second measurement gave +28.1. A solution of the purified amide that had been made from the lactone, containing 0.405 g in 50 cc solution, rotated 0.90° to the right at 20° in a 4 dcm tube with sodium light; hence $[\alpha]_D^{20} = +27.8$. The average of the three measurements, +28.0, is taken as the specific rotation of the pure amide.

It is interesting to observe that the molecular rotations of the amides of α-*d*-mannoheptonic, *d*-galactonic, and *l*-arabonic acids have the same sign and nearly the same numerical values.

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[44] Quotation from Hudson and Monroe, Jour. Am. Chem. Soc., **41**, 1140; 1919.

[45] Untersuchungen über Kohlenhydrate und Fermente, p. 300.

TABLE 22.—*Rotation of three amides of similar terminal configuration*

Amide	Configuration	Specific rotation	Molecular[1] rotation
α-*d*-Mannoheptonic	$CH_2OH \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{O}{CNH_2}$	+28.0	+63.0(10)[2]
d-Galactonic	$CH_2OH \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{O}{CNH_2}$	+30.2	+58.9(10)[2]
l-Arabonic	$CH_2OH \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{O}{CNH_2}$	+37.9	+62.5(10)[2]

[1] The molecular weights of the three amides are 225, 195, and 165.

The cause of this agreement evidently lies in the fact that the three structures have the same configurations for the α-, β-, and γ-carbon atoms near the amide groups. In an accompanying article by Hudson and Komatsu it is shown that the principle of optical superposition holds fairly closely for such amides as these and that the α- and β-carbon atoms are the only ones that have much influence on the rotation.

III. RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP

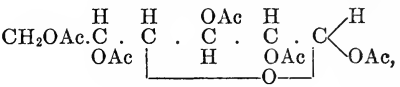
1. THE HALOGENO-ACYL AND NITRO-ACYL DERIVATIVES OF THE ALDOSE SUGARS[46]

The extensive use of bromo-acetyl glucose in the accomplishment of syntheses in the sugar group makes the knowledge of its structure a matter of prime importance. At the present time it is considered to be a derivative of the β form of the sugar and is designated β-bromo-acetyl glucose. In accordance with this view it is to be supposed that an isomeric α-bromo-acetyl glucose can exist, derivable from the α form of the hexose. Fischer and Armstrong[47] reported a description of two such forms of bromo-acetyl, likewise of chloro-acetyl glucose, but Fischer's later work[48] in which he was unable to reproduce the preparation of the α forms of these compounds shows either that some detail of vital importance was not definitely recognized in the earlier research, or that the supposed α isomers were only impure crystals of the common β forms.[49] The discovery of these so-called α forms, isomeric with the common β-halogeno-acetyl glucoses, will unquestionably open a rich field of synthetic exploration in the sugar group. Since any evidence which relates to the constitution and properties of these compounds may be useful in aiding the attainment of their synthesis, the following comparison of the rotatory powers of various halogeno-acyl sugars is presented. Anticipating some of the conclusions it may be stated that Van't

[46] C. S. Hudson, Jour. Am. Chem. Soc., **46**, 462-467; 1924.
[47] Fischer and Armstrong, Ber., **34**, 2885; 1901.
[48] Fischer, Ber., **44**, 1898; 1911.
[49] Kurt Hoesch, "Emil Fischer, sein Leben und sein Werk," Verlag Chemie, 1921, p. 353. Emil Fischer, "Aus meinen Leben," J. Springer, Berlin, 1923, p. 197.

Hoff's hypothesis of additive optical superposition holds, as a first approximation at least, among the halogeno-acyl aldoses and that there is clear proof, based upon the application of this principle, that the common bromo-acetyl and chloro-acetyl glucoses are not β compounds, as now accepted, but are α derivatives.

Consider the rotatory powers of the constituent asymmetric carbon atoms of the α and β forms of glucose penta-acetate, the structural formulas of which are generally believed to be



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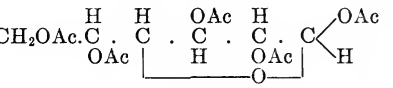
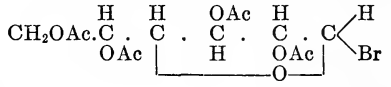


(Ac = CH_3-CO)

Let the rotation of the terminal asymmetric carbon atom be written $+A_{Ac}$ for the α form and $-A_{Ac}$ for the β modification and let the rotation of the remainder of the molecule, the acetylated basal chain that is common to both forms, be written $B_{glucose}$. The molecular rotation of the α form is then $(B_{glucose}+A_{Ac})$, that of the β form is $(B_{glucose}-A_{Ac})$ and the value of $B_{glucose}$ is one-half the sum of the molecular rotations, that is, $[(B_{glucose}+A_{Ac})+(B_{glucose}-A_{Ac})]\div 2 = B_{glucose}$.[50]

Bromo-acetyl glucose, which has been isolated with certainty in only one form, probably can exist in two modifications having structures similar to those of the glucose penta-acetates, namely,



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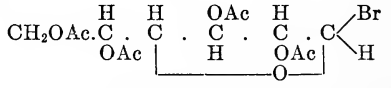


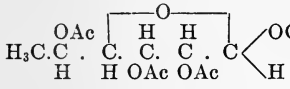
the molecular rotations of which may be written $(B_{glucose}+A_{Br})$ and $(B_{glucose}-A_{Br})$, respectively. Subtracting $B_{glucose}$ from these leaves in the one case A_{Br} and in the other $-A_{Br}$, which shows that the numerical value of A_{Br} can be obtained from the rotations of the two glucose penta-acetates and the one known form of bromo-acetyl glucose without a knowledge of whether the bromo compound is an α or a β derivative. Similar calculations may be applied to the rotations of chloro-acetyl glucose, iodo-acetyl glucose, nitro-acetyl glucose and the recently discovered fluoro-acetyl glucose,[51] as these compounds have the structure of bromo-acetyl glucose with the bromine atom replaced by chlorine, iodine, nitrate radical, or fluorine,

[50] Hudson, Jour. Am. Chem. Soc., **31**, 66; 1909.
[51] Brauns, ibid., **45**, 833; 1923.

respectively; and last, the calculations may be applied to the similar derivatives of other aldose sugars. We are thus in position to learn the values of the rotation of the terminal asymmetric carbon atom in the bromo-acetyl (A_{Br}), chloro-acetyl (A_{Cl}), iodo-acetyl (A_I), nitro-acetyl (A_{NO_3}), and fluoro-acetyl (A_F) aldose sugars. An example will indicate how these values are calculated from the data recorded in the accompanying two tables. Fluoro-acetyl xylose, for instance, shows a molecular rotation $[M]_D = (B_{xylose} + A_F) = +18{,}600$ (Table 24) and the rotation of the acetylated basal chain of xylose is $B_{xylose} = +10{,}200$ (Table 23), hence $A_F = ([M]_D - B_{xylose}) = +8{,}400$.

From the data recorded in the last two columns of Table 24 it may be concluded that the rotation of the end asymmetric carbon atom of a halogeno-acetyl or nitro-acetyl aldose is approximately a constant quantity for the various aldoses. The nitro group and each halogen give rise to the respective values: $A_{NO_3} = 37{,}100$, $A_F = 9{,}800$, $A_{Cl} = 37{,}900$, $A_{Br} = 59{,}300$, and $A_I = 85{,}400$.

The rotations of certain of the substances mentioned in the tables require discussion. The value of the acetylated basal chain of *l*-rhamnose, $B_{l\text{-rhamnose}} = -1{,}100$ (Table 23), is obtained as half the sum of the molecular rotations of the α and β forms of tri-acetyl-methyl-*l*-rhamnoside recently described by Fischer, Bergmann, and Rabe, which probably have the structures,



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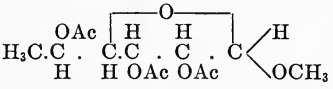


The negative sign for A_{Br} for bromo-acetyl rhamnose should not be considered exceptional; it is explained by the fact that rhamnose is a levo sugar having the configuration of a reduced *l*-mannose. Since the other compounds of Table 24 belong to the *d*-series, a systematic comparison should refer to derivatives of the dextro rather than the levo form of rhamnose and as the rotations of these compounds must be equal in magnitude and opposite in sign to the recorded rotations of the *l*-rhamnose derivatives the value of A_{Br} that will be obtained from them must be $+58{,}600$, which agrees not only in magnitude but also in sign with the values of A_{Br} shown by the other sugars.

The value of A_{Cl} for the first chloro-acetyl galactose and that of A_{NO_3} for nitro-acetyl galactose are based upon $B_{galactose} = +25{,}400$, from Table 23, because these substances and the β-galactose penta-acetate from which they may be prepared presumably have a butylene oxide ring in common. While the value for A_{NO_3} is normal, that of A_{Cl} is exceptionally high and the reason is not apparent. The value of A_{Cl} for chloro-acetyl mannose is exceptionally low, and it has been omitted in taking the average value of A_{Cl}. The value of A_{Cl} for chloro-acetyl lactose is somewhat low and should be reexamined.

Mention may here be made that the chloro-acetyl and bromo-acetyl derivatives of *l*-arabinose, a sugar closely related in configuration to *d*-galactose, likewise show exceptional rotations, $[\alpha]_D = -225$ and -283, respectively, in chloroform solution.[52] The α and β tetra-acetates of *l*-arabinose[53] show $[\alpha]_D = +42$ and $+147$, respectively, in chloroform; hence, $B_{l\text{-arabinose}}$ is $(42+147)318 \div 2 = 30{,}100$, and the specific rotations of the α and β forms of chloro-acetyl-*l*-arabinose are calculated, using the value of $A_{Cl} = 37{,}800$ from Table 24, to be $(30{,}100 - 37{,}800) \div 294 = -26$, and $(30{,}100 + 37{,}800) \div 294 = 231$, respectively, and those of the two forms of bromo-acetyl-*l*-arabinose to be -86 and $+264$. While the magnitudes of the rotations that are recorded by Chavanne agree fairly well with those calculated (-225 instead of $+231$ and -283 instead of $+264$), the signs are just opposite; this complete disagreement obviously requires further experimental study.

The measurement of the rotation of bromo-acetyl galactose ($[\alpha]_D = +236$) by Fischer and Armstrong[54] has not been included in the table because benzene was used as the solvent, and such solutions frequently

TABLE 23.—*The values of the quantity B, the rotation of the acetylated basal chain, for various fully acetylated aldose sugars*

Substance	$[\alpha]_D$ in chloroform	Molecular rotation	B=half the sum of the molecular rotations
α-*d*-glucose penta-acetate [1]	+102	+39,800	+20,700 ($B_{glucose}$)
β-*d*-glucose penta-acetate (mol. wt. 390)	+4	+1,600	
α-*d*-mannose penta-acetate	+55	+21,400	+5,800 ($B_{mannose}$)
β-*d*-mannose penta-acetate (mol. wt. 390)	−25	−9,800	
α-*d*-galactose penta-acetate	+107	+41,700	+25,400 ($B_{galactose}$)
β-*d*-galactose penta-acetate (mol. wt. 390)	+23	+9,000	
α-*d*-xylose tetra-acetate	+89	+28,300	+10,200 (B_{xylose})
β-*d*-xylose tetra-acetate (mol. wt. 318)	−25	−7,900	
α-*d*-maltose octa-acetate	+122	+82,700	+62,700 ($B_{maltose}$)
β-*d*-maltose octa-acetate (mol. wt. 678)	+63	+42,700	
α-*d*-lactose octa-acetate	+54	+36,600	+16,900 ($B_{lactose}$)
β-*d*-lactose octa-acetate (mol. wt. 678)	−4	−2,700	
α-*d*-cellobiose octa-acetate	+41	+27,800	+8,800 ($B_{cellobiose}$)
β-*d*-cellobiose octa-acetate (mol. wt. 678)	−15	−10,200	
TO THESE ARE APPENDED FOR LATER REFERENCE			
4th galactose penta-acetate	+61	+23,800	+3,700 ($B'_{galactose}$)
3d galactose penta-acetate (mol. wt. 390)	−42	−16,400	
α-methyl *l*-rhamnoside tri-acetate [2]	−53	−16,100	−1,100 ($Bl_{rhamnose}$)
β-methyl *l*-rhamnoside tri-acetate [2] (mol. wt. 304)	+46	+14,000	

[1] The references for the fully acetylated sugars are (*a*) Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 1270; 1915, (lactose); (*b*) **37**, 1276; 1915, (cellobiose and maltose); (*c*) **37**, 2748; 1915, (xylose); (*d*) **38**, 1224; 1916, (galactose). (*e*) Hudson and Dale, ibid., **37**, 1264; 1915, (glucose); (*f*) **37**, 1280; 1915. (mannose).

[2] Fischer, Bergmann and Rabe, Ber., **53**, 2362 (1920). The rotations were measured in acetylene tetrachloride, $CHCl_2.CHCl_2$, but their values in chloroform, $CHCl_3$, are probably nearly the same. See note 13 of Table 24.

[52] Chavanne, Compt. rend., **134**, 661; 1902.

[53] Hudson and Dale, Jour. Am. Chem. Soc., **40**, 992; 1918.

[54] Fischer and Armstrong, Ber., **35**, 833; 1902.

rotate quite at variance from those made with chloroform; however, the value is approximately what would be expected.

Iodo-tetra-acetyl galactose has been prepared by Unna[55] in crystalline form, but its rotation is not recorded. The substance melted at 88° and was quite unstable, decomposing in a short time, even in a vacuum desiccator.

TABLE 24.—*The values of the quantity A, the rotation of the end asymmetric carbon atom, for the halogeno-acetyl and nitro-acetyl aldose sugars*

Substance	Molecular weight	$[\alpha]_D$ in $CHCl_3$	Molecular rotation $[M]_D$	Rotation of end carbon [1] $A=[M]_D-B$	Av. A
Fluoro-acetyl xylose [2]	278	+67	+18,600	+8,400	+9,800 (A_F)
Fluoro-acetyl glucose [2]	350	+90	+31,500	+10,800	
Fluoro-acetyl cellobiose [2]	638	+30	+19,100	+10,300	
Chloro-acetyl xylose [3]	295	+165	+48,700	+38,500	+37,900 (A_{Cl}) (Excluding the value for chloro-acetyl mannose).
Chloro-acetyl glucose [4]	367	+166	+60,900	+40,200	
Chloro-acetyl mannose [5]	367	+90	+33,000	+27,200	
Chloro-acetyl lactose [6]	655	+72	+47,200	+30,300	
Chloro-acetyl maltose [7]	655	+159	+104,100	+41,400	
Chloro-acetyl cellobiose [8]	655	+73	+47,800	+39,000	
Bromo-acetyl xylose [9]	339	+212	+71,900	+61,700	+59,300 (A_{Br})
Bromo-acetyl glucose [10]	411	+198	+81,400	+60,700	
Bromo-acetyl cellobiose [11]	699	+96	+67,100	+58,300	
Bromo-acetyl lactose [12]	699	+105	+73,400	+56,500	
Iodo-acetyl glucose [12, 13]	458	+232	+106,300	+85,600	+85,400 (A_I)
Iodo-acetyl cellobiose [11]	746	+126	+94,000	+85,200	
Nitro-acetyl glucose [14]	393	+149	+58,600	+37,900	+37,100 (A_{NO_3})
Nitro-acetyl galactose [15]	393	+153	+60,100	+34,700	
Nitro-acetyl maltose [16]	681	+149	+101,500	+38,800	
TO THESE ARE APPENDED FOR SPECIAL DISCUSSION LATER					
Bromo-acetyl *l*-rhamnose [17]	353	−169	−59,700	−58,600	
First chloro-acetyl galactose [18]	367	+212	+77,800	+52,400	
Second chloro-acetyl galactose [19]	367	−78	−28,600	−32,300	

[1] The values of B are taken from Table 23, each sugar having its own value. For galactose there are two values of B, derived respectively from the two pairs of penta-acetates; in the later discussion the grounds for choosing between these in particular cases are indicated.

[2] Brauns, Jour. Am. Chem. Soc., **45**, 833; 1923.

[3] Hudson and Johnson, Jour. Am. Chem. Soc., **37**, 2748; 1915.

[4] von Arlt, Monatsh., **22**, 147; 1901.

[5] Brauns, Jour. Am. Chem. Soc., **44**, 401; 1922.

[6] Bodart, Monatsh., **23**, 5; 1902.

[7] Schliephacke, Ann., **377**, 186; 1910. Foerg, Monatsh., **23**, 44; 1902.

[8] Schliemann, Ann., **378**, 374; 1911. Skraup and Geinsperger [Monatsh., **26**, 1470; 1905] found +74.9 in chloroform.

[9] Dale, Jour. Am. Chem. Soc., **37**, 2746; 1915.

[10] Koenigs and Knorr, Ber., **34**, 962; 1901.

[11] Fischer and Zemplén, Ber., **43**, 2536; 1910.

[12] E. Fischer and H. Fischer, Ber., **43**, 2521; 1910.

[13] The rotation of iodo-acetyl glucose was measured in acetylene tetrachloride but the rotation in chloroform is probably about the same since iodo-acetyl cellobiose rotates 126 and 123 in these solvents and bromo-acetyl lactose rotates 105 in both of them.

[14] Koenigs and Knorr, Ber., **34**, 976; 1901.

[15] Ibid., p. 978.

[16] Ibid., p. 4343.

[17] Fischer, Bergmann, and Rabe, Ber., **53**, 2362; 1920. The rotation was measured in acetylene tetrachloride. See footnote 13.

[18] Skraup and Kremann, Monatsh., **22**, 380; 1901.

[19] Hudson and Johnson, Jour. Am. Chem. Soc., **38**, 1226; 1916.

[55] Unna, Dissertation, "Synthese einiger neuer Galactoside," Berlin, 1911, p. 20.

(a) CLASSIFICATION OF THE HALOGENO-ACETYL AND NITRO-ACETYL DERIVATIVES OF THE ALDOSE SUGARS AS ALPHA OR BETA FORMS ON THE BASIS OF THEIR ROTATORY POWERS

The second chloro-acetyl galactose (Table 24) is a derivative of the third galactose penta-acetate and doubtless the two substances possess the same internal oxygen ring. Since the butylene ring has been assigned to the first and second penta-acetates and the first chloro-acetate of galactose some other ring must be assumed for the structure of the second chloro-acetyl galactose and its parent penta-acetate. Whatever ring this may be [56] it doubtless also occurs in the fourth galactose penta-acetate since the third and fourth penta-acetates establish an equilibrium in acetic anhydride solution containing zinc chloride. On the basis of their rotations the third and fourth penta-acetates are β and α forms, respectively, and the value of the rotation of the acetylated basal chain common to them is (Table 24) $B'_{galactose} = +3{,}700$. The value of A_{Cl} for the second chloro-acetyl galactose is then (Table 24) $([M]_D - B'_{galactose}) = -28{,}600 - 3{,}700 = -32{,}300$, which agrees in magnitude with the average value of A_{Cl} from Table 24 (37,900), but differs in sign. Since galactose belongs to the dextro series, this negative sign is not a result of the convention used in naming the sugar derivatives, as was the case with the derivatives of *l*-rhamnose that have already been discussed. It may be explained, however, on the hypothesis that the molecular rotation of the second chloro-acetyl galactose is not $(B'_{galactose} + A_{Cl})$ but rather $(B'_{galactose} - A_{Cl})$, which means that the second chloro-acetyl galactose is a representative of an opposite type (α or β) from the first chloro-acetyl galactose that gives a positive value for A_{Cl}. By this it is not assumed that the two chloro-acetyl galactoses are an α,β pair with a common ring, but rather that one is an α form of a certain ring type and the other a β form of a second ring structure. If we follow the system of nomenclature which the writer suggested [57] in 1909, now in general use, and name the more dextrorotatory form of an α,β pair in the *d*-series the α form, the second chloro-acetyl galactose must be designated a β compound since A_{Cl} for it has a negative value. Likewise, the first chloro-acetyl galactose and all the other halogeno-acetyl and nitro-acetyl aldose sugars that are listed in Table 24 must be classsed as α derivatives, bromo-acetyl rhamnose being thus α-bromo-acetyl-*l*-rhamnose. The evidence upon which these compounds have been classed as β derivatives in the past consists solely in the fact that they yield β glucosides or β acetates when the halogen or nitro group is replaced

[56] E. F. Armstrong, [The Simple Carbohydrates and Glucosides, Longmans, Green & Co., 3d ed., 1919, p. 26] has assigned provisionally an ethylene oxide ring to these compounds. I regard this structure as representing only one of the possible rings and am of the opinion that the question is still an open one, awaiting the production of new experimental evidence.

[57] Hudson, Jour. Am Chem. Soc., **31**, 72; 1909.

(synthesis of Koenigs and Knorr).[58] This evidence is, however, worthless because of the frequent occurrence of a Walden inversion during such replacements. In 1911 Emil Fischer [59] called attention to this possibility with the remark that "In the past the configuration which has been assigned to the halogeno-acetyl glucoses is that of the (β) glucosides that may be prepared from them. I would remark that the latest observations on the frequency of the occurrence of a change in configuration during a substitution on the asymmetric carbon atom [60] render this conclusion very unsafe. Possibly in this connection it should not be overlooked that the halogeno-acetyl glucoses rotate strongly to the right in opposite sign to the rotation of the β glucosides that may be prepared from them."

Additional evidence that the halogeno-acetyl and nitro-acetyl sugars of Table 24 (with the exception of the second chloro-acetyl galactose) are α rather than β compounds, is the increase in dextrorotation of the end asymmetric carbon atom with increasing weight of the attached group. This is strikingly shown in the regular progression, $A_F = +9{,}800$, $A_{Cl} = 37{,}900$, $A_{Br} = +59{,}300$, $A_I = +85{,}400$, which is the direction of change that is to be expected for a series of α compounds. A similar series of β compounds, for example, the numerous β glucosides, always shows the opposite direction of change of A with increasing weight of the attached group.[61] Thus, the specific rotations of the β glucosides of urea, methylurea, dimethylurea, and phenylurea are -24, -30, -33, and -55, respectively, showing a progression in the levo direction which is even more pronounced if the molecular rotations are compared.

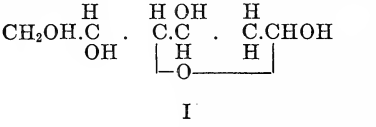
In the case of nitro-acetyl glucose it appears that the α and β forms may both have been prepared in crystalline condition. Skraup and Kremann [62] report the existence of a crystalline nitro-acetyl glucose, of specific rotation $+1.5$ in chloroform, and mention that it readily isomerizes on recrystallization from alcohol to the stable form of specific rotation $+149$ mentioned in Table 24. If these forms do constitute an α,β pair of common ring structure, which seems probable because of the apparently easy transformation, the well-known stable isomer must be named the α form on account of its higher dextrorotation, thus confirming the conclusion previously reached. The calculated specific rotation in chloroform of the β-nitro-acetyl glucose is $(B_{glucose} - A_{NO_3}) \div \text{mol. wt.} = (20{,}700 - 37{,}100) \div 393 = -42$, a value which suggests that Skraup and Kremann's preparation may have contained some of the α form.

[58] Koenigs and Knorr, Ber., **34**, 962; 1901.
[59] Ref. 48. See also Fischer, Ber., **43**, 2521; 1910. Fischer and von Mechel, Ber., **49**, 2813; 1916.
[60] E. Fischer, Ann., **381**, 123; 1911.
[61] Hudson, Jour. Am. Chem. Soc., **31**, 84; 1909.
[62] Skraup and Kremann, Monatsh, **22**, 1043; 1901.

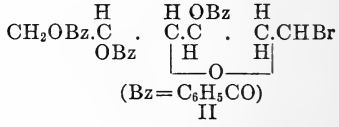
Chloro-acetyl maltose has a specific rotation of +159 in chloroform Table (24) and we have shown that it is the α form. The rotation of the corresponding β form is calculated to be $(B_{maltose} - A_{Cl}) \div$ mol. wt. $= (62{,}700 - 37{,}900) \div 655 = +38$. Freudenberg and Ivers [63] have recently described a chloro-acetyl maltose which they prepared by the action of a solution of hydrogen chloride in ether on maltose octa-acetate. Its specific rotation in chloroform was to the right, +67.5. On first sight it seems possible that the substance may be the unknown β form (new nomenclature) of chloro-acetyl maltose containing some of the α form, but Freudenberg and Ivers found that the percentage of chlorine in it corresponded with the formula of a chloro-*octa*-acetyl maltose better than with that of a chloro-*hepta*-acetyl derivative. The present considerations are therefore given with reserve, but in their support it may be mentioned that the theoretical difference of the chlorine content for the two substances is less than 0.5 per cent.

(b) CLASSIFICATION OF VARIOUS ACYL AND HALOGENO-ACYL DERIVATIVES OF THE ALDOSES

(1) The Value of A_{Br} for Bromo-Tribenzoyl-Glucodesose.—It is possible to calculate the value of A_{Br} for this derivative of glucodesose from the rotations of some compounds that have been described recently by Bergmann, Schotte, and Leschinsky.[64] From glucodesose, the structure of which is I,



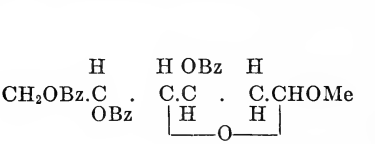
I



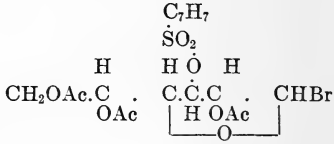
(Bz = C_6H_5CO)

II

they prepared the tetra-benzoate and from it bromo-tri-benzoyl-glucodesose, of structure II, showing $[\alpha]_D = +121$ in acetylene tetrachloride. From this bromo compound (mol. wt., 539) they prepared tri-benzoyl-methyl-glucodesoside, of Structure III.



III



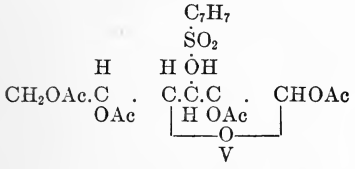
IV

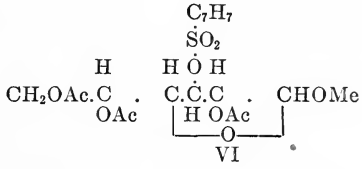
showing $[\alpha]_D = -34.3$ in acetylene tetrachloride. The molecular rotation of III (mol. wt., 490) may be written, on the very probable assumption that the substance is a β-glucoside from analogy with the similarly prepared derivatives of other sugars, $(B_{glucodesose} - A_{Me}) = (-34.3)\ 490 = -16{,}800$. The value of A_{Me} is half the differ-

[63] Freudenberg and Ivers, Ber., **55**, 941; 1922.
[64] Bergmann, Schotte and Leschinsky, Ber., **56**, 1052; 1923.

ence of the molecular rotations of the α and β forms of methyl-glucoside tetra-acetate, which has been found to be[65] +26,900; hence $B_{glucodesose} = +10{,}100$. The molecular rotation of bromo-tri-benzoyl-glucodesose (II) may be written $(B_{glucodesose} + A_{Br}) = (121)\ 539 = +65{,}200$: hence, subtracting the value of $B_{glucodesose}$, $A_{Br} = +55{,}100$. This agrees with the values of A_{Br} shown in Table 24 and indicates that the principle of optical superposition may be applied to the derivatives of glucodesose. It also proves that the bromo compound is an α form and that the glucodesoside that is prepared from it is a β derivative. Glucodesose thus conforms with glucose in these reactions.

(2) The Value of A_{Br} for Bromo-tri-acetyl-toluenesulfo Glucose.—From this derivative of glucose, of Structure IV, of molecular weight 523 and specific rotation +164 in acetylene tetrachloride, Freudenberg and Ivers[66] have prepared tetra-acetyl-toluenesulfo glucose, of Structure V,



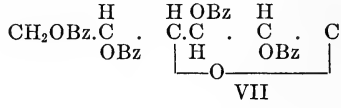


of molecular weight 502 and specific rotation +13.6 in acetylene tetrachloride, and likewise tri-acetyl-toluenesulfo-methyl glucoside, of Structure VI, of molecular weight 474, and specific rotation −17.1 in the same solvent. The molecular rotation of V may be written, on the probable assumption that it is a β compound from the method of its synthesis, $(B_x - A_{Ac}) = (13.6)\ 502 = +6{,}800$. The value of A_{Ac} is one-half the difference between the molecular rotations of the α and β forms of glucose penta-acetate, which is known[65] to be 19,100; hence $B_x = +25{,}900$. The molecular rotation of IV may be written $B_x + A_{Br} = (164)\ 523 = +85{,}800$ (Equation (I)), and hence $A_{Br} = +59{,}900$, in good agreement with previous values. In a similar manner the molecular rotation of VI may be written $B_x - A_{Me} = (-17.1)\ 474 = -8{,}100$, and subtracting the value of A_{Me} previously mentioned (26,900) leaves $B_x = +18{,}800$. Using this value of B_x in Equation (I) gives $A_{Br} = +67{,}000$. While the agreement here is not so good as in the case of the acetate the result leaves no doubt that again the bromo compound is an α derivative and the acetate and glucoside are both β forms.

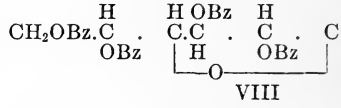
(3) The Value of A_{Br} for Bromo-tetra-benzoyl Glucose.—The specific rotation of this substance (mol. wt., 659) was measured by

[65] Hudson and Dale, Jour. Am. Chem. Soc., **37**, 1264; 1915.
[66] Freudenberg and Ivers, Ber., **55**, 941; 1922.

Fischer and Helferich [67] in toluene solution, $[\alpha]_D = +145$. They state that the compound is quite soluble in chloroform, but no measurement of the rotation in this solvent is recorded. In the usual manner they prepared from it tetra-benzoyl-methyl glucoside (mol. wt., 610), showing $[\alpha]_D = +31$ in chloroform. The structure of the bromo compound is doubtless VII,



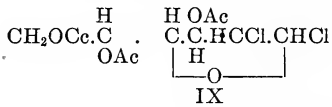
VII



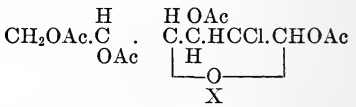
VIII

and that of the glucoside, VIII. Writing the molecular rotation of the glucoside, VIII, which is assumed to be a β form on account of its production from a bromo-acyl sugar, $[M]_D = B_y - A_{Me} = (31)\ 610 = +18{,}900$, and using the value of $A_{Me} = +26{,}900$ previously mentioned, B_y is $+45{,}800$. Writing the molecular rotation of the bromo compound VII, $B_y + A_{Br} = (145)\ 659 = +95{,}600$, and subtracting the value of B_y leaves $A_{Br} = +49{,}800$, which indicates by its normal magnitude and sign that the bromo compound is an α form and the glucoside a β derivative. For a more accurate measurement of the value of A_{Br} it is necessary that the rotation of the bromo compound be measured in chloroform solution.

(4) The Value of A_{Cl} for Tri-acetyl-(1,2)dichloro Glucose (Tri-acetyl-glucal Dichloride).—From this crystalline addition product of chlorine to glucal, of Structure IX

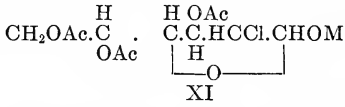


IX

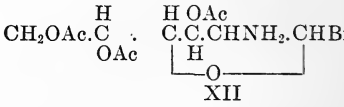


X

of molecular weight 343, and of specific rotation +200 in acetylene tetrachloride, Fischer, Bergmann and Schotte [68] prepared tetra-acetyl-2-chloro glucose (tetra-acetyl-glucose-2-chlorohydrin), of Structure X, of molecular weight 367, and of specific rotation +51 in acetylene tetrachloride, and also triacetyl-2-chloro-methyl-glucoside (tri-acetyl-methyl-glucoside-2-chlorohydrin), of Structure XI,



XI



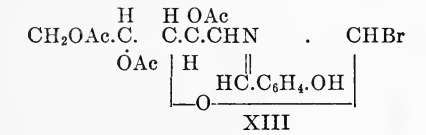
XII

of molecular weight 339 and of specific rotation +40 in acetylene tetrachloride. In these compounds the space positions of the hydrogen and chlorine atoms about carbon 2 are not yet known, but since X and XI were prepared from IX the configuration of this carbon

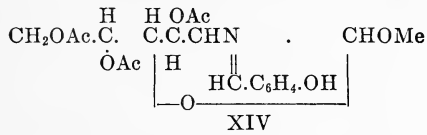
[67] Fischer and Helferich, Ann., **383**, 68; 1911.
[68] Fischer, Bergmann, and Schotte, Ber., **53**, 509; 1920.

atom is the same in the three substances or, in other words, they have the same basal chain, and consequently the usual method of calculation of A_{Cl} may be applied to their rotations. Assuming from the method of their preparation that X and XI are β forms, the molecular rotation of X is $B_w - A_{Ac} = (51)\ (367) = +18{,}700$, and $B_w = 18{,}700 + 19{,}100 = 37{,}800$. The molecular rotation of XI is $B_w - A_{Me} = (40)\ (339) = +13{,}600$ and $B_w = 13{,}600 + 26{,}900 = +40{,}500$. The average of these two values of B_w is $+39{,}100$. The molecular rotation of IX is $B_w + A_{Cl} = (200)\ (343) = 68{,}600$, and subtracting the average value of B_w leaves $A_{Cl} = +29{,}500$. This value is in fair agreement with those previously obtained for A_{Cl}, proving that the dichloro compound, IX, is an α form, and that its acetate (X) and methyl glucoside (XI) are β derivatives.

(5) The Value of A_{Br} for an Acyl Derivative of Glucosamine, 1-Bromo-2-salicylidene-3,5,6-tri-acetyl-glucosamine.—By condensing bromo-tri-acetyl-glucosamine,[69] of Structure XII, with salicyl aldehyde, Irvine and Hynd [70] prepared a crystalline substance which Irvine and Earl [71] have lately shown to be a salicylidene derivative, of Structure XIII,



XIII



XIV

Its molecular weight is 471 and its $[\alpha]_D$ in methyl alcoholic solution is $+242$. From it Irvine and Earl have prepared in the usual way a methyl glucosidic derivative (mol. wt. 422, and $[\alpha]_D = +76$ in methyl alcohol), of Structure XIV. Assuming as before that the substitution of the bromine atom by the methoxy group yields in this case a β-glucoside, the molecular rotation of XIV is $(B_s - A_{Me}) = (76)\ (422) = +32{,}100$, and $B_s = +32{,}100 + 26{,}900 = +59{,}000$. Writing the molecular rotation of the bromo compound XIII $(B_s + A_{Br}) = (242)\ (471) = +114{,}000$, and subtracting the value of B_s leaves $A_{Br} = +55{,}000$ in methyl alcoholic solution. This value conforms fairly well with those of A_{Br} in Table 24; possibly a better agreement will be found when the rotations in chloroform are measured,

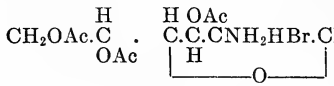
[69] (*a*) Irvine, McNicoll, and Hynd, Jour. Chem. Soc., **99**, 250; 1911. (*b*) Hamlin, Jour. Am. Chem. Soc., **33**, 766; 1911. The configuration of the second carbon, $CHNH_2$, for glucosamine is not known with certainty.

[70] Irvine and Hynd, Jour. Chem. Soc., **103**, 41; 1913.

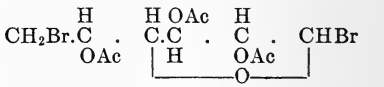
[71] Irvine and Earl, ibid., **121**, 2370; 1922.

but the present data show clearly that these salicylidene compounds of glucosamine fall in line with the general observation that the bromo compound is an α form and the methyl glucoside derivative a β modification. The principle of optical superposition apparently applies to very diverse derivatives of glucosamine; in addition to its application to these salicylidene derivatives, it is to be recalled that Irvine and Earl have shown that the α and β forms of glucosamine hydrochloride differ in molecular rotation in water by +16,160, conforming closely with the similar difference for the α and β forms of glucose, +16,920, and Hudson and Dale [72] have shown that the α and β forms of glucosamine penta-acetate show nearly the same difference in molecular rotation in chloroform (+35,900) as do the α and β forms of glucose penta-acetate (+38,100). Irvine and Earl have expressed the view that these agreements may be taken to indicate a closer structural relationship of glucosamine to glucose than to mannose because the similar difference for the forms of mannose penta-acetate is considerably less (+31,200).

(6) The Value of A_{Br} for Bromo-tri-acetyl-glucosamine Hydrobromide.—The conclusion from the preceding section that bromo-tri-acetyl-glucosamine yields a salicylidene derivative which is an α form makes it very probable that the parent substance is likewise an α modification because a change from α to β on carbon atom 1 would not be expected in this condensation which takes place on carbon atom 2. Better evidence, leading to the same result, may be obtained from a comparison of the rotation of bromo-tri-acetyl-glucosamine with those of the glucosamine α- and β-penta-acetates. If the rotation of bromo-tetra-acetyl-glucosamine were known in chloroform solution an accurate determination of A_{Br} for this important compound, which is the parent substance for the known aldosides of glucosamine, could be obtained by the usual comparison with the glucosamine penta-acetates. I can find no record of the preparation of this substance, but the specific rotation of bromo-tri-acetyl-glucosamine hydrobromide (mol.wt., 449) is given by Irvine, McNicoll and Hynd [73] as +136° in pure dry acetone, increasing during two hours to the constant final value of 148. The question of the nature of this mutarotation will be discussed later; for the present the final value +148 will be taken as the specific rotation of bromo-tri-acetyl-glucosamine hydrobromide, of Structure XV. The molecu-



XV



XVI

[72] Hudson and Dale, Jour. Am. Chem. Soc., **38**, 1431; 1916.
[73] Jour. Chem. Soc., **99**, 250; 1911.

lar rotation of the compound is $(B_t + A_{Br}) = (148)\ (449) = +66{,}500$, and I assume, as a first approximation, that the molecular rotation of its acetyl derivative has the same value. This is made very probable by the fact that the molecular rotations of the hydrochloride and hydrobromide of methyl glucosamine [74] are almost exactly alike (Irvine and Hynd), and those of the similar halide salts of 6-amino-methyl-glucoside (Fischer and Zach [75]) are likewise almost identical in value. The rotation of the acetylated basal chain of glucosamine, which is here assumed to have the same value as in the hydrobromide derivatives, is one-half the sum of the molecular rotations of the α- and β-glucosamine penta-acetates, or $B_t = +18{,}400$ (in chloroform solution).[76] Subtracting this value from the value 66,500 found in the equation above $A_{Br} = 48{,}100$, which indicates that bromo-tri-acetyl-glucosamine is an α form.

TABLE 25.—*Classifications on the basis of rotatory power*

Alpha forms	$[\alpha]_D$	Beta forms	$[\alpha]_D$
The known halogeno-acetyl derivatives of xylose, glucose, mannose, rhamnose, lactose, maltose, and cellobiose		The second chloro-acetyl galactose	−78
		Tri-benzoyl-methyl-glucodesoside	−34
		Tetra-acetyl-toluenesulfo glucose	+13.6
The known stable nitro-acetyl derivatives of glucose, galactose, and maltose		Tri-acetyl-toluenesulfo-methyl-glucoside	−17.1
		Tetra-benzoyl-methyl-glucoside	+31
The first chloro-acetyl galactose	+212	Tetra-acetyl-2-chloro glucose	+51
Bromo-tri-benzoyl glucodesose	+121	Tri-acetyl-2-chloro-methyl-glucoside	+40
Bromo-tri-acetyl-toluenesulfo glucose	+164	1-Methyl-2-salicylidene-3,5,-6 - tri - acetyl-glucosamine	+76
Bromo-tetra-benzoyl glucose	+145		
Tri-acetyl-(1,2)-dichloro glucose	+200		
Bromo-tri-acetyl-glucosamine hydrobromide	+148		
1-Bromo-2-salicylidene-3,5,6-tri-acetyl-glucosamine	+242		

The slight mutarotation of this substance when dissolved in pure dry acetone, from 136 to 148, mentioned previously, is very noteworthy. Possibly it is caused by a slow combination with the solvent. Another possibility is that the crystalline substance, which seems to be the α form of high dextrorotation, may have contained a small amount of the unknown β form, which changed slowly to the α form in solution, or again the solid material may have been the β form, this having changed so rapidly in solution to the α form that only the last portion of the mutarotation was observed. The subject must be discussed with caution as the existing experimental evidence is capable of various interpretations and additional data are much to be desired.

Summarizing this section and the previous one, the classifications of Table 25 have been made on the basis of rotatory power.

[74] This compound seems to be of a different type of structure from methyl glucoside, the methyl radical being attached to the nitrogen atom, but this abnormality does not affect the present argument since the peculiar grouping is present in both the hydrochloride and the hydrobromide.

[75] Fischer and Zach, Ber., **44**, 132; 1911.

[76] Hudson and Dale, Jour. Am. Chem. Soc., **38**, 1434; 1916.

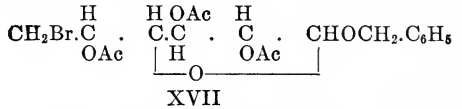
The values for the rotations of the terminal asymmetric carbon atom now know for so many types of derivatives allow the calculation of the rotations of a large number of halogeno-acyl, nitro-acyl and mixed acyl derivatives of various sugars and glucosides. It does not seem desirable to burden the literature with these calculated values, as the typical examples which have been given will illustrate the method of applying the appropriate coefficients in particular cases. However, I wish to record the calculated rotations of three substances which are of immediate interest.

(c) THE CALCULATED ROTATION OF β-CHLORO-ACETYL GLUCOSE

This is the unknown isomer of the common, or α-chloro-acetyl glucose. Its specific rotation in chloroform is calculated to be $[\alpha]_D = (B_{glucose} - A_{Cl}) \div \text{mol. wt.} = (20{,}700 - 37{,}800) \div 366 = -47°$. In like manner the specific rotation in chloroform of the unknown β-bromo-acetyl glucose is calculated to be $[\alpha]_D = (B_{glucose} - A_{Br}) \div \text{mol. wt.} = (20{,}700 - 59{,}300) \div 411 = -94°$. Amé Pictet and Castan [77] have lately prepared by the action of strong hydrochloric acid on glucosan an amorphous substance which they name α-glucosyl chloride and have stated that on acetylation it yielded the long sought β-chloro-acetyl glucose (new nomenclature), and that on treatment with sodium methylate it yielded α-methyl-glucoside. No rotations of any of these substances were recorded and the identifications were made from melting-point determinations alone; under these conditions a definite conclusion as to whether the unknown β-chloro-acetyl glucose was really obtained can not be made and the question must await the production of more accurate experimental evidence.

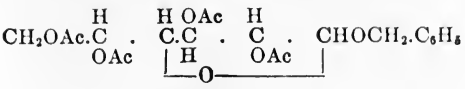
(d) THE CALCULATED ROTATION OF 1,6-DIBROMO-TRI-ACETYL GLUCOSE (ACETO-1,6-DIBROMO GLUCOSE)

This substance was discovered by Fischer and Armstrong and has been used by Fischer as the starting point of many syntheses, but there appears to be no record of a measurement of its specific rotation. The value can be calculated from the rotation of 1-benzyl-2,3,5-tri-acetyl-6-bromo glucose (XVII) which was synthesized by Fischer and Zach.[78] The structure of aceto-1,6-dibromo glucose is XVI. By the interaction of XVI with benzyl alcohol, the corresponding acyl-benzyl-glucoside was produced, of Structure XVII, mol. wt. 459 and $[\alpha]_D = -47$ in chloroform



XVII

[77] Amé Pictet and Castan, Helv. Chim. Acta, **4**, 319; 1921.
[78] Fischer and Zach, Ber., **45**, 456; 1912.



XVIII

solution. Now the specific rotation of tetra-acetyl-benzyl-glucoside, of Structure XVIII and mol. wt. 438, has been found by Fischer and Helferich to be $[\alpha]_D = -50$ in alcoholic solution. This acetylated glucoside was prepared from bromo-acetyl glucose by Koenigs and Knorr's method and is doubtless a member of the β-glucosidic series, which is confirmed by the fact of the easy hydrolysis by emulsin of the benzyl glucoside that is produced from it after the removal of the acetyl groups. Writing the molecular rotation of XVIII accordingly $(B_{glucose} - A_x) = -50\ (438) = -21{,}900$, and substituting the value of $B_{glucose}$ (from Table 23) in this equation leaves $A_x = 42{,}600$. The molecular rotation of XVII, doubtless also a β compound on account of its synthesis by Koenigs and Knorr's method, is written $(B'_{glucose} - A_x) = (-47)\ (459) = -21{,}600$ and subtracting A_x leaves $B'_{glucose} = 21{,}000$. Then the specific rotation of XVI becomes $(B'_{glucose} + A_{Br}) \div$ mol. wt. $= (21{,}000 + 59{,}300) \div 474 = +169$ [79] on the probable view that the substance is an alpha derivative. It is desirable for this calculation to know the specific rotation of XVIII in chloroform rather than in alcohol.

(e) CALCULATION OF THE ROTATION OF BROMO-ACETYL GENTIOBIOSE

As there is much evidence that the biose of amygdalin may be gentiobiose,[80] and the synthesis of amygdalin is likely to be accomplished accordingly through bromo-acetyl gentiobiose, the specific rotation of this substance is here calculated. The molecular rotation of the acetylated basal chain of gentiobiose ($B_{gentiobiose}$) is one-half the sum of the molecular rotation in chloroform of the α and β forms of gentiobiose octa-acetate, or $(+52-5)\ 678 \div 2 = 15{,}900$.[81] The specific rotation of α-bromo-acetyl gentiobiose may be written $(B_{gentiobiose} + A_{Br}) \div$mol. wt. $= (15{,}900 + 59{,}300) \div 699 = +108$ in chloroform.[82]

In concluding, I express the hope that others may assist as occasion presents itself in revising to higher accuracy the large amount of data that are considered in this article. For the extension of this method of treatment of constitutional questions in the sugar group it is desirable that the rotations of new substances be measured in water or in chloroform solution.

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[79] This calculated rotation should be +186, see p. 345.

[80] Haworth and Leitch, Jour. Chem. Soc., **121**, 1921; 1922. Kuhn, Ber., **56**, 857; 1923. See also number 3 of the present series of articles, Jour. Am. Chem. Soc., **46**, 483; 1924.

[81] Hudson and Johnson, Jour. Am. Chem. Soc., **39**, 1272; 1917.

[82] Subsequently Zemplén has crystallized this compound and found $[\alpha]_D = +112$ in chloroform, see p. 347.

2. THE HALGENO-ACETYL DERIVATIVES OF A KETOSE SUGAR (*d*-FRUCTOSE) [83]

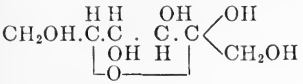
In article 1 it was shown that Van't Hoff's hypothesis of additive optical superposition holds for many diverse types of acyl derivatives of the various aldose sugars. In seeking to determine the applicability of this principle to similar compounds of the ketose sugars one meets the difficulty that only a few such derivatives have ever been prepared. The number of known crystalline ketoses is itself rather small, fructose, sorbose, tagatose, perseulose, manno-keto-heptose, and sedoheptose making up the list, and for only one of them, namely fructose, have acyl derivatives been described in sufficient number to permit a test of the principle. D. H. Brauns has prepared fructose tetra-acetate,[84] two chloro-acetyl fructoses,[85] and quite recently he has described fluoro-acetyl and bromo-acetyl fructose.[86] Hudson and Brauns [87] have described a methyl fructoside and its tetra-acetate, and two penta-acetates of fructose, and Hudson and Yanovsky [88] have prepared β-fructose in pure condition. From a comparison of the structures and rotations of these substances a substantial beginning can be made in applying the principle of optical superposition to the ketoses and their acyl derivatives. The method of comparison is that which has been used in article 1.

(a) THE ROTATIONS OF BETA-FRUCTOSE AND BETA-METHYL FRUCTOSIDE

Pure crystalline β-fructose, so designated [89] because it exhibits mutarotation in the dextro direction, shows $[\alpha]_D^{20} = -133$ in aqueous solution. By acetylating this crystalline substance at low temperature with acetic anhydride and zinc chloride Brauns prepared crystalline tetra-acetyl fructose in good yield; $[\alpha]_D^{20}$ was -91.6 in chloroform solution.[90] The methylation of this tetra-acetate by Purdie and Irvine's method (with methyl iodide and silver oxide) yielded crystalline tetra-acetyl methyl fructoside of $[\alpha]_D^{20} = -125$ in chloroform solution, and the removal of the acetyl groups from the latter compound by alkali yielded crystalline methyl fructoside, of $[\alpha]_D^{20} = -172$ in water. The last substance was known to be a fructoside because it did not reduce Fehling's solution. As its rotation is more levo than that of β-fructose it was designated β-methyl fructoside, and its tetra-acetate and the fructose tetra-acetate which was used in the methylation were accordingly also allocated to the β series.

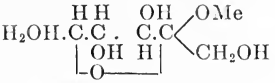
[83] C. S. Hudson, Jour. Am. Chem. Soc., **46**, 477; 1924.
[84] Brauns, Verslag. Akad. Wetenschappen Amsterdam, 1908, p. 577. See also Jour. Am. Chem. Soc., **37**, 2736; 1915.
[85] Brauns, Jour. Am. Chem. Soc., **42**, 1846; 1920.
[86] Brauns, ibid., **45**, 2381; 1923.
[87] Hudson and Brauns, ibid., **38**, 1216; 1916; **37**, 1283, 2736; 1915.
[88] Hudson and Yanovsky, ibid., **39**, 1013; 1917.
[89] Hudson, Jour. Am. Chem. Soc., **31**, 77; 1909.
[90] Private communication from Doctor Brauns.

These synthetical relations appear to give a series of β compounds starting with β-fructose and ending with its β-methyl fructoside, and it is almost certain that the four members of the series have the same ring structure. While the position of the ring is not known, it will be written for the sake of definiteness as a butylene linkage with the understanding that the present argument really does not involve any assumption of the location of this ring and would apply without change in case the ring is in some other than the butylene position. The structures of β-fructose and β-methyl fructoside are written



I. β-Fructose

and



II. β-Methyl fructoside

and the molecular rotation of I is $(b'_{fructose} - a'_{OH})$, where a'_{OH} represents the rotation of carbon 2, the asymmetric carbon at the right-hand end of the ring, and $b'_{fructose}$ designates the rotation of the remainder of the structure, comprising asymmetric carbon atoms 3, 4, and 5. In similar manner the molecular rotation of II is $(b'_{fructose} - a'_{Me})$, and the difference of the molecular rotations of I and II is then $(b'_{fructose} - a'_{OH}) - (b'_{fructose} - a'_{Me}) = a'_{Me} - a'_{OH}$. Compare the similar difference for β-glucose and its β-methyl glucoside; their molecular rotations may be written $(B'_{glucose} - A'_{OH})$ and $(B'_{glucose} - A'_{Me})$ respectively, and the difference is $(A'_{Me} - A'_{OH})$.

TABLE 26.—*Comparison of the molecular rotations of β-glucose, β-fructose, and their β-methyl glucosidic derivatives*

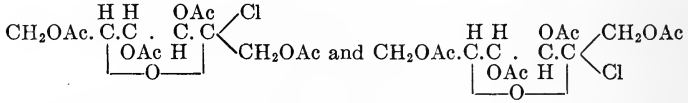
Substance	Molecular weight	$[\alpha]_D^{20}$ in water	$[M]_D^{20}$	Difference
β-d-Glucose	180	+19	+3,400	+9,600=$(A'_{Me} - A'_{OH})$
β-d-Methyl glucoside	194	−32	−6,200	
β-d-Fructose	180	−133	−23,900	+9,500=$(a'_{Me} - a'_{OH})$
β-d-Methyl fructoside	194	−172	−33,400	

The difference is the same in both magnitude and sign for the ketose and the aldose. From independent evidence which will be presented in the next section it is probable that $A'_{Me} = a'_{Me}$ and $A'_{OH} = a'_{OH}$. If such is the case, the substitution of $-CH_2OH$ for $-H$ on asymmetric carbon atom 2 does not change the rotation. On the other hand, the equality that is proved by the values in Table 26 would still hold provided the indicated substitution caused the same change of rotation in both β-fructose and its methyl fructoside.

(b) THE ROTATIONS OF THE TWO CHLORO-ACETYL FRUCTOSES

Brauns has prepared from tetra-acetyl fructose two isomeric chloro-acetyl fructoses which he has provisionally designated as α and β forms of the same ring structure. As it will appear from what follows that Brauns's allocations should be reversed, it seems desirable

to designate provisionally the one having $[\alpha]_D^{20} = -161$ in chloroform as the first chloro-acetyl fructose, and the one having $[\alpha]_D^{20} = +45$ in chloroform as the second chloro-acetyl fructose. The first chloro-acetyl fructose was made from fructose tetra-acetate by the action of acetic anhydride with phosphorus pentachloride and aluminum chloride, while the second one resulted when the aluminum chloride was omitted. In agreement with Brauns it is here assumed that the isomers constitute an α,β pair and their structures are written with the same ring that was assumed for the parent tetra-acetate, thus,



III. First chloro-acetyl fructose. IV. Second chloro-acetyl fructose.

Their molecular rotations are written ($a_{fructose} - a_{Cl}$) and ($a_{fructose} + a_{Cl}$), the meaning of the symbols being apparent from what precedes. One-half the difference of these molecular rotations is a_{Cl}, which gives the value of a_{Cl} for an acetylated ketose and permits a comparison with the value of the similar A_{Cl} for the aldoses, which was found in article 1 to be about +37,800.

The value of a_{Cl} for the ketose is the same in both magnitude and sign as that of A_{Cl} for the aldoses. This is good evidence that the substitution of $-CH_2OAc$ for $-H$ does not change the rotation of carbon atom 2. Since the second chloro-acetyl fructose is more dextrorotatory than the first one it should be designated the α form and the first one the β form, thus reversing the naming which Brauns provisionally proposed.

TABLE 27.—*Comparison of a_{Cl} for a ketose (d-fructose) with A_{Cl} for the aldoses*

Substance	Molecular weight	$[\alpha]_D^{20}$ in $CHCl_3$	$[M]_D^{20}$	A_{Cl}	A_{Cl} for the aldoses	$a_{fructose}$[1]
Second chloro-acetyl fructose (α form)	367	+45	+16,500	+37,800	+37,900	−21,200
First chloro-acetyl fructose (β form)	367	−161	−59,100			

[1] The rotation under this heading is one-half the sum of the molecular rotations of column four, and is here appended for later reference.

(c) THE ROTATIONS OF FLUORO-ACETYL AND BROMO-ACETYL FRUCTOSE

In considering the rotations of these compounds the calculations are made slightly differently, following a method that was used frequently in article 1. Brauns prepared the substances from β-fructose penta-acetate (see below) which is a derivative in its turn of the fructose tetra-acetate previously mentioned. They probably have the same structure as the first (or β) chloro-acetyl fructose, III with the Cl atom replaced by F or by Br; the proof of this allocation will appear in the calculations. The rotation of the acetylated basal

chain of fructose is one-half the sum of the molecular rotations of the first and second chloro-acetyl fructoses, $a_{fructose} = [(a_{fructose} + a_{Cl}) + (a_{fructose} - a_{Cl})] \div 2 = -21{,}200$ (see Table 27). Since the molecular rotation of fluoro-acetyl fructose is more negative than $a_{fructose}$ (see Table 28), the substance should be designated a β form and its rotation written $(a_{fructose} - a_F)$, and similarly the rotation of bromo-acetyl fructose becomes $(a_{fructose} - a_{Br})$. From the values of these rotations the coefficient a_F and a_{Br} are obtained, and in Table 28 they are recorded in comparison with the similar values for the aldose derivatives.

TABLE 28.—*Comparison of the values of a_F and a_{Br} for a ketose (d-fructose) with the similar values for the aldoses*

Substance	Molecular weight	$[\alpha]_D^{20}$ in $CHCl_3$	$[M]_D^{20}$	$a_{fructose} - [M]_D^{20}$	Aldose coefficients
Fluoro-acetyl fructose	350	−90	−31, 500	+10, 500 (a_F)	+9, 800 (A_F)
Bromo-acetyl fructose	411	−189	−77, 700	+56, 500 (a_{Br})	+59, 300 (A_{Br})

Here again the derivatives of the ketose show the same coefficients as do those of the aldoses. In further support of the conclusion that the fluoro-acetyl and bromo-acetyl fructoses and the first chloro-acetyl fructose are β compounds it is observed that the rotation of the end asymmetric carbon atom increases in the levo direction with increasing weight of the halogen, the three values being $-a_F = -9{,}800$, $-a_{Cl} = -37{,}800$, and $-a_{Br} = -56{,}500$, whereas the similar progression for the halogeno-acetyl glucoses, which belong to the α series (see article 1), is a change in the dextro direction. This independent method of deciding the assignment of compounds to the α or β series is here emphasized as it will be used in later articles in some cases where other methods can not be applied.

(d) THE ROTATION OF BETA-TETRA-ACETYL METHYL FRUCTOSIDE

The $[\alpha]_D^{20}$ of this compound, which has been mentioned previously, is −125 in chloroform and its molecular weight is 362. Its structure is that of II with the four hydroxyl groups replaced by acetate groups, and accordingly its molecular rotation is written $(a_{fructose} - a_{Me}) = (-125)\ 362 = -45{,}200$. Subtracting $a_{fructose}$ (−21,200) gives $a_{Me} = 24{,}000$, which is in fair agreement with the value of $A_{Me} = 26{,}900$, obtained in article 1 for the aldose series.

(e) THE ROTATIONS OF THE TWO ISOMERIC PENTA-ACETATES OF FRUCTOSE

By analogy with the halogeno-acetyl compounds of fructose it is to be expected that two fructose penta-acetates can exist, having the structures of III and IV with the chlorine atom replaced by an acetate group. The rotations of these compounds will now be calculated

and the results compared with the rotations of the two fructose penta-acetates that Hudson and Brauns have described. Since the values of a_F, a_{Cl}, and a_{Br} in the fructose group have been found to be equal to the corresponding values for the aldose group it seems safe to assume that $a_{ac} = A_{ac} = +19{,}100$ from article 1. The molecular rotation of α-fructose penta-acetate (mol. wt., 399) then becomes $a_{fructose} + a_{ac} = -21{,}200 + 19{,}100 = -2{,}100$; that of β-fructose penta-acetate $-21{,}200 - 19{,}100 = -40{,}300$ and the $[\alpha]_D^{20}$ values for the two substances become $-2{,}100 \div 399 = -5$ and $-40{,}300 \div 399 = -103$, respectively, in chloroform. The two known penta-acetates of fructose show $[\alpha]_D^{20} = +34.7$ and -121 in chloroform, respectively. It seems very unlikely that the dextrorotatory penta-acetate can be the expected α-form; possibly it has a ring structure different from that of the compounds hitherto considered. The other known penta-acetate, of $[\alpha]_D^{20} = -121$, may be the expected β form, though the difference of 18° in specific rotation makes such a conclusion uncertain. The fact that the fluoro-acetyl and bromo-acetyl fructoses, the rotations of which fit in normally in the calculations, were prepared by Brauns from this penta-acetate seems good evidence that it is the expected β form. Further study of these penta-acetates and the conversion of the halogeno-acetyl fructoses into penta-acetates will doubtless clear up the present uncertainty.

(f) DISCUSSION OF THE CONCLUSIONS

While the derivatives of fructose have been shown to yield the same coefficients for the rotations of carbon atom 2 as do the aldose derivatives for their similarly constituted carbon atom 1, in another respect they differ markedly from aldose compounds, and this difference will doubtless be found to be a general characteristic of ketose derivatives. Reference is made to the exhibition of mutarotation. Fructose itself mutarotates, as do the aldoses. But fructose tetra-acetate does not exhibit this change, though glucose tetra-acetate does, and likewise it has not been possible to change either penta-acetate of fructose to an isomeric form by heating in acetic anhydride containing zinc chloride, a reaction which proceeds readily with the similar aldose acetates. This difference makes the synthesis of acyl compounds of fructose quite a different problem from that of the aldose derivatives. Thus the known levorotatory penta-acetate of fructose, which has been allocated to the β series, can not be transformed by this reaction to its expected α isomer. The other known penta-acetate, of dextrorotation, was made from fructose tetra-acetate by the action of acetic anhydride and sulfuric acid, a method of preparation that gives little evidence regarding the structure of the substance.

It has been shown in article 1 that in the aldose series the known halogeno-acetyl derivatives are α compounds, with the one exception

of the second chloro-acetyl galactose, which is a β form. In the ketose series, as represented by fructose, the known fluoro-acetyl and bromo-acetyl fructoses are β compounds, while for chloro-acetyl fructose both the α and β forms have been prepared. Brauns has remarked on the great difference in stability between α-chloro-acetyl fructose and its β isomer, the chlorine in the α form being much more firmly held. He has also emphasized that bromo-acetyl fructose, which has now been shown to be a β derivative, is a very unstable substance. By analogy one may expect that α-bromo-acetyl fructose will be more stable than its known isomer, and it seems possible that α-iodo-acetyl fructose might be of sufficient stability to permit its preparation, whereas Brauns' experience with β-bromo-acetyl fructose makes it doubtful whether β-iodo-acetyl fructose could be prepared, since the iodo-acetyl sugars are, in general, less stable than the bromo compounds.

This greater stability of the α forms has a bearing on the question of the structure of the chloro-acetyl maltose that Freudenberg has described as a chloro-octa-acetyl maltose. In article 1 it was suggested that this substance may be the expected β-chloro-hepta-acetyl maltose, since its rotation approaches the calculated value and the analytical data make a distinction between the hepta and octa acetate rather uncertain. Freudenberg emphasized that the substance is very reactive, exchanging its chlorine atom much more easily than the known chloro-acetyl maltose. On comparing this behavior with that of β-chloro-acetyl fructose it does not appear anomalous and is indeed what would be expected of β-chloro-acetyl maltose.

3. THE BIOSE OF AMYGDALIN (GENTIOBIOSE) AND ITS CONFIGURATION [91]

Haworth and Leitch [92] have recently applied Irvine's method of methylation and subsequent hydrolysis to the old problem of the determination of the structure of the biose of amygdalin, the glucoside of bitter almonds. It has long been known that the amygdalin molecule is composed of two molecules of *d*-glucose and one of *l*-mandelonitrile,

$$\underset{\text{(amygdalin)}}{C_{20}H_{27}O_{11}N} + 2\ H_2O = 2\ \underset{\text{(}d\text{-glucose)}}{C_6H_{12}O_6} + \underset{\text{(}l\text{-mandelonitrile)}}{C_6H_5.CHOH.CN}$$

By methylating amygdalin with dimethyl sulphate and sodium hydroxide solution it was transformed to the methyl ester of hepta-methyl amygdalinic acid and this crystalline substance yielded on acid hydrolysis (1) *d,l*-mandelic acid, (2) 2,3,5,6-tetramethyl glucose, and (3) a trimethyl glucose which was shown to have the methyl

[91] C. S. Hudson, Jour. Am. Chem. Soc., **46**, 483–489; 1924.
[92] Haworth and Leitch, Jour.Chem. Soc., **121**, 1921; 1922.

groups on carbons 2, 3, and 5. The occurrence of racemic mandelic acid is explained by the racemizing and subsequent saponifying action of alkali on the *l*-mandelonitrile grouping in amygdalin. The tri- and tetramethyl glucoses that were found were the same substances that Haworth and Leitch [93] had previously isolated through the hydrolysis of fully methylated maltose, a fact which led them to express the conclusion:

The disaccharide of amygdalin has therefore the structure of maltose and quite definitely can not be cellobiose. For the stereochemical formulation of this maltose structure we are dependent on the researches of other workers on the selective action of enzymes, and here the results, if not conflicting, are certainly anomalous. Their results favor the view that the amygdalin biose is a glucose α-glucoside * * * and therefore, on this reasoning, the biose itself must be maltose and amygdalin is mandelonitrile α-maltoside * * * . Should it ultimately be the case that the stereochemical representation of the biose is found to be that of a glucose β-glucoside, this can not, of course, affect the structural formula we have herein ascribed to the sugar, but it may point to the identity of the amygdalin biose with isomaltose or gentiobiose.

Supplementary evidence relating to the structure of the biose of amygdalin has been published quite recently by Kuhn,[94] who has applied E. F. Armstrong's method [95] of hydrolyzing a glucoside by an enzyme and observing the direction of the mutarotation of the liberated sugar. It will be recalled that Armstrong thus showed that the α and β forms of methyl glucoside liberate α- and β-glucose, respectively. Kuhn now shows that the two glucose molecules that are liberated during the hydrolysis of each molecule of amygdalin are both β-glucose, and he concludes that the biose of amygdalin is a β-glucosido glucose. Adopting the maltose linkage (1 to 6) which has been proved by Haworth and Leitch for both maltose and the biose of amygdalin and considering both glucose residues to have the structure of β-glucose the configuration of amygdalin is to be written [96]

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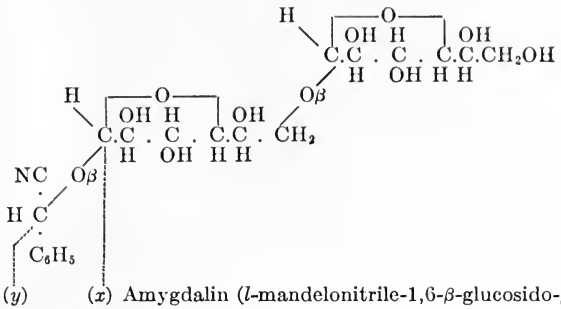
[93] Haworth and Leitch, ibid., **115**, 809; 1919.

[94] Kuhn, Ber., **56**, 857; 1923.

[95] Armstrong, Jour. Chem. Soc., **83**, 1305; 1903.

[96] This configurational formula is the one which Kuhn has published with the exception that I have reversed the configuration of the *l*-mandelonitrile residue. The symbols (*x*) and (*y*) designate two carbon atoms which will later be subjects of discussion. The configuration here assigned to *l*-mandelonitrile is obtained from a consideration of the fact that the change from *l*-mandelic acid, which results from the saponification of *l*-mandelonitrile, to *l*-mandelamide is accompanied by a change of rotation in the dextro direction. This evidence, attention to which has been called by Freudenberg, Brauns, and Siegel [Ber., **56**, 193; 1923], seems fully trustworthy. In a previous article [Jour. Am. Chem. Soc., **40**, 813; 1918] I have shown that the dextrorotatory amides of the acids of the sugar group have their α-OH on the right of the chain and the levorotatory ones have it on the left, and from this rule I deduced configurations for the two mandelic acids. My conclusions should, however, be reversed because I overlooked the significance of the fact that the mandelic acids are strongly rotatory in distinction from the weakly rotatory acids of the sugar group. Freudenberg has corrected my configurations and has shown that the rule which I proposed is to be considered a special case of the more general relation that the change of the rotation of an α-hydroxy acid to that of its amide is in the dextro direction when the α-OH is on the right of the chain, the carboxyl group being written at the top, and in the levo direction when it is on the left of the chain. This form of the rule is similar to that which I have proposed [Jour. Am. Chem. Soc., **39**, 462, Footnote 3; 1917] in the case of the acids and lactones of the sugar group.

The configuration that is assigned to the β-glucose in the amygdalin formula is that which has been proposed by Böeseken [Ber., **46**, 2612; 1913] and supported by Brigl [Z. Physiol. Chem., **122**, 245; 1922] from independent evidence.



(*y*) (*x*) Amygdalin (*l*-mandelonitrile-1,6-β-glucosido-β-glucoside)

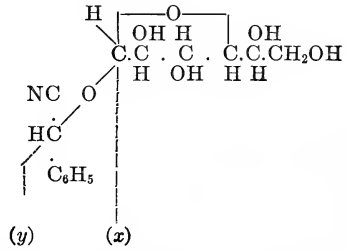
Although the work of Haworth and Leitch, supplemented by the evidence that Kuhn has adduced, shows the configuration of amygdalin, the problem of the identity of the biose remains unsolved. Cellobiose has been excluded by Haworth and Leitch's results, as they have shown that it possesses a 1 to 5 linkage, while Kuhn's experiments have excluded maltose (an α-glucosido glucose), and while the biose may be isomaltose or gentiobiose, as stated by Haworth and Leitch, it may also be some undiscovered β-glucosido glucose. It is at this point that the following evidence from polarimetric data is presented, which shows clearly that the biose of amygdalin is gentiobiose. The proof of this identification is the fact, which will now be established, that the rotation of the biose chain of amygdalin, as calculated from the rotations of two derivatives of amygdalin, namely, isoamygdalin and prulaurasin, has the same value as the rotation of the chain of gentiobiose. It will be seen from the calculations that this evidence is entirely independent of that of Haworth and Leitch and likewise of that of Kuhn, and that the combining of the results of these three lines of evidence proves the configuration of gentiobiose to be that of 1,6-β-glucosido glucose. Maltose and gentiobiose are thus shown to be the α- and β-glucosidic forms, respectively, of 1,6-glucosido glucose; they constitute the first α,β pair of compound sugars to be definitely allocated.

(*a*) THE RELATIONSHIP OF AMYGDALIN TO ISO-AMYGDALIN AND PRULAURASIN

If the carbon atom marked (*y*) in the formula for amygdalin were symmetric it would be possible to apply to amygdalin the same method of calculation of its rotatory power that was used by Hudson and Johnson [97] to calculate the rotation of β-methyl gentiobioside. In that case the calculated $[\alpha]_D^{20}$ was $-38°$, in good agreement with the observed value, $-36°$. But the carbon (*y*) is asymmetric and its rotation is unknown. To get around the difficulty, advantage is taken of the fact that the *l*-mandelonitrile group in amygdalin is readily racemized by alkali, the remainder of the structure of the

[97] Hudson and Johnson, Jour. Am. Chem. Soc., **39**, 1272; 1917.

glucoside being unchanged, so that a new compound results, the iso-amygdalin of Dakin,[98] which is a mixture in nearly equal quantities of amygdalin (*l*-mandelonitrile bioside) and the corresponding *d*-mandelonitrile bioside. The last-named substance has been crystallized from *iso*-amygdalin by Krieble [99] who speaks of it as *d*-amygdalin; this designation seems inappropriate and it is preferable to use the name neo-amygdalin previously proposed by Tutin,[1] who prepared its hepta-acetate in pure condition. A parallel series of three similar glucosides has been obtained in the same way by starting with *l*-mandelonitrile glucoside, a substance which Fischer prepared from amygdalin by the hydrolyzing action of yeast on the union between the two glucose molecules. Fischer's glucoside [prunasin] has the configuration



and is *l*-mandelonitrile β-glucoside. In alkaline solution its nitrile group racemizes [2] and a mixture of *l*- and *d*-mandelonitrile glucosides results. The mixture is the natural glucoside *prulaurasin* which Hérissey [3] isolated from the fresh leaves of *prunus laurocerasus*. Pure *d*-mandelonitrile glucoside is identical with the natural *sambunigrin* which Bourquelot and Danjou [4] isolated from the leaves of *sambucus nigra*.

(b) THE ROTATORY POWERS OF THE GLUCOSIDES OF THE AMYGDALIN GROUP

For the present calculations it is desirable to know with accuracy the rotations of iso-amygdalin (*d,l*-mandelonitrile β-bioside) and prulaurasin (*d,l*-mandelonitrile β-glucoside). It is assumed that the racemization of the nitrile group causes carbon (*y*) in their structures to be without rotation, an assumption which allows the calculations to be made. In Table 29 the values which have been accepted for the specific rotations of the six glucosides in question are recorded from the literature, and the data from which the values have been selected are stated in the footnotes.

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[98] Dakin, Jour Chem. Soc., **85**, 1512; 1904. See also Walker, ibid., **83**, 472; 1903.
[99] Krieble, Jour. Am. Chem. Soc., **34**, 716; 1912.
[1] Tutin, Jour. Chem. Soc., **95**, 663; 1909.
[2] Caldwell and Courtauld, Jour. Chem. Soc., **91**, 666, 671; 1907.
[3] Hérissey, Jour. Pharm. Chim., [6] **23**, 5; 1906.
[4] Bourquelot and Danjou, ibid., [6] **22**, 219, 385; 1906.

TABLE 29.—*The rotations of the glucosides of the amygdalin group*

Substance	Molecular weight	$[\alpha]_D^{20}$ in water	$[M]_D^{20}$ in water
Hexosides:			
l-Mandelonitrile *β*-glucoside (Fischer's glucoside)	295	[1]−27	−8,000
d,l-Mandelonitrile *β*-glucoside (prulaurasin)	295	[2]−52	−15,300
d-Mandelonitrile *β*-glucoside (sambunigrin)	295	[3]−76	−22,400
Biosides:			
l-Mandelonitrile *β*-gentiobioside (amygdalin)	457	[4]−38.5	−17,600
d,l-Mandelonitrile *β*-gentiobioside (iso-amygdalin)	457	[5]−50.5	−23,100
d-Mandelonitrile *β*-gentiobioside (neo-amygdalin)	457	[6]−61	−27,900

[1] Fischer [Ber., **28** 1508; 1895] found $[\alpha]_D^{20} = -26.9$ and -26.8 for the glucoside which he made by the action of the enzymes of yeast on amygdalin. Fischer and Bergmann [Ber., **50,** 1047; 1917] found −27.0 for the substance which they prepared synthetically. The accepted value −27 seems certain within less than 0.5°.

[2] Prulaurasin is doubtless a mechanical mixture. Hérissey found values of $[\alpha]_D$ ranging from −52.6 to −54.6, for the product which he isolated from *prunus laurocerasus*. Caldwell and Courtauld found −52.7 for the product made by the action of weak alkali on Fischer's glucoside, and Fischer and Bergmann found values ranging between −51.9 and −55.7 for the product which they synthesized. The average of the values for Fischer's glucoside (−27) and sambunigrin (−76, see below) is −51.5, which seems more trustworthy than the other values. The value −52 is accepted as probably correct within 1° for an equimolecular mixture of Fischer's glucoside and sambunigrin.

[3] Bourquelot and Danjou found −76.3 and −75.4 for the glucoside which they isolated from the leaves of *sambucus nigra*, and Fischer and Bergmann found −75.1 and −76.3 for the product which they synthesized. The accepted value −76 seems correct within 0.5°.

[4] While Fischer's glucoside, prulaurasin and sambunigrin are anhydrous substances, amygdalin crystallizes with three molecules of water. Caldwell and Courtauld's (Ref. 2, p. 673) value of −35.5 for this trihydrate (mol. wt., 511) corresponds to −39.7 for anhydrous amygdalin (mol. wt., 457). Auld [Jour. Chem. Soc., **93,** 1277; 1908] found −41.6, Schiff [Ber., **32,** 2701; 1899] −40.5, and Tutin −37.8 and −38.0 for the anhydrous substance. As Caldwell and Courtauld and Tutin clearly understood the nature of the partial racemization of amygdalin by alkali, a change which increases the levorotation, and apparently used much care in their measurements, their values are here accepted and the average −38.5 taken as probably correct within 0.5°, for anhydrous amygdalin.

[5] Dakin's value for iso-amygdalin dihydrate (mol. wt., 493) is −47.6, corresponding to −51.3 for the anhydride. The average of the accepted values for amygdalin and neoamygdalin is −49.7, and the average of this and Dakin's value is −50.5, which seems probably correct within one degree.

[6] This is Krieble's value for anhydrous neo-amygdalin (Ref. 99, p. 727). The rotation varies considerably with the concentration and the temperature and this value is interpolated from Krieble's data. It is probably correct within 2°.

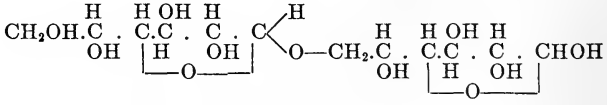
(c) CALCULATION OF THE ROTATION OF THE BIOSE OF AMYGDALIN

Referring to the structural formula of amygdalin, let N represent the rotation of carbon (y), the asymmetric carbon of the *l*-mandelonitrile residue, let A represent that of carbon (x), and let X represent that of the remainder of the structure, the basal chain of the biose. The molecular rotation of amygdalin is then $(N+A+X)$. For neo-amygdalin the molecular rotation is $(-N+A+X)$, while for iso-amygdalin, which is assumed to be a mixture of equal parts of amygdalin and neo-amygdalin, the molecular rotation is $[(N+A+X)+(-N+A+X)]\div 2 = A+X = -23{,}100$, from Table 29. Referring now to the structure of Fischer's glucoside, let N' represent the rotation of carbon (y), A that of carbon (x), and B that of the remainder of the structure, the basal chain of glucose. The molecular rotation of Fischer's glucoside is then $(N'+A+B)$, that of sambunigrin is $(-N'+A+B)$ and that of their equimolecular mixture, prulaurasin, is $[(N'+A+B)+(-N'+A+B)]\div 2 = A+B = -15{,}300$, from Table 29. Now the value of B, the basal chain of glucose, is known accurately from the molecular rotations of the α and β forms of *d*-glucose to be $+11{,}900$;[5] hence $A = -15{,}300 - 11{,}900 = -27{,}200$. Substitut-

ing this value of A in the first equation of this section, gives $X = -23{,}100 + 27{,}200 = +4{,}100$ as the value of the molecular rotation of the basal chain of the amygdalin biose. As this sugar must unquestionably belong to the class of reducing sugars and be capable of existing in α and β forms, it is necessary, in order to be in a position to identify the sugar, to calculate the rotations of these forms by adding in one case and subtracting in the other the value of the rotation of the end asymmetric carbon atom of the reducing aldoses, which is known accurately for glucose as one-half the difference of the molecular rotations of its α and β forms, $+8{,}500$. The molecular and specific rotations in water of the α and β forms of the biose (mol. wt., 342) of amygdalin are thus calculated to be:

α Form of the biose, $[M]_D^{20} = +4{,}100 + 8{,}500 = +12{,}600$, $[\alpha]_D^{20} = +37°$
β Form of the biose, $[M]_D^{20} = +4{,}100 - 8{,}500 = -4{,}400$, $[\alpha]_D^{20} = -13°$

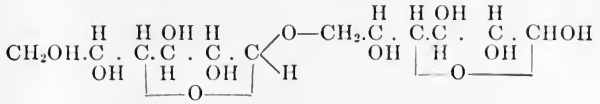
There are three known crystalline gluco-bioses of the reducing sugar type, namely, maltose, cellobiose, and gentiobiose, and a fourth, isomaltose, which has not been obtained crystalline. The specific rotations of β-maltose and β-cellobiose are $+118$ and $+16$, respectively; hence neither of these sugars can be the biose of amygdalin. The stable rotation of isomaltose is about $+60$, which indicates that its β form must be much more dextrorotatory than is β-cellobiose, as the stable rotation of cellobiose is $+35$; this conclusion definitely excludes isomaltose as a possibility. On the other hand, crystalline β-gentiobiose rotates [6] approximately $-11°$, a value which agrees within the limits of error with the calculated value for the β form of the amygdalin biose. Amygdalin thus becomes *l-mandelonitrile-β-gentiobioside*, of the configuration which Haworth and Leitch and Kuhn have proved. In consequence, the structure of gentiobiose is now shown to be that of maltose, the two disaccharides possessing the same 1,6 linkage between their constituent glucose molecules. The difference between them consists in the stereochemical positions, maltose being *1,6-α-glucosido glucose* and gentiobiose being *1,6-β-glucosido glucose*. Their configurations are as follows, the formula for maltose being quoted from Haworth and Leitch.



1,6- α-glucosido glucose (maltose)

[5] Hudson, Jour. Ind. Eng. Chem., **8**, 379; 1916. This is one-half the sum of the molecular rotations (mol. wt. 180) of the two forms, of $[\alpha]_D^{20} = 113$ and 19, respectively.

[6] Bourquelot and Hérissey, Jour. Pharm. Chim., 6, **16**, 418; 1902. Hudson, Jour. Am. Chem. Soc., **38**, 1566; 1916. The stable rotation is $+9.8°$. The value -11 seems probably correct within 3°.



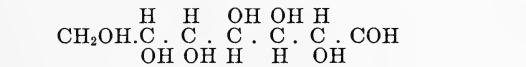
1,6- β-glucosido glucose (gentiobiose)

Maltose and gentiobiose thus constitute the first known α, β pair of compound sugars to be definitely allocated. Some deductions from this allocation will be discussed in a subsequent article.

Finally, mention may be made that the present proof of the identity of the biose of amygdalin with gentiobiose points the way to the synthesis of amygdalin and also to the preparation of gentiobiose from amygdalin. One should expect the synthesis to start with β-gentiobiose octa-acetate and proceed through the conversion of this to a halogeno-acetyl gentiobiose,[7] which can doubtless be united with ethyl mandelate and the synthesis continued to amygdalin by the same reactions through which Fischer and Bergmann [8] have synthesized Fischer's glucoside, prulaurasin and sambunigrin from bromo-acetyl glucose and ethyl mandelate. To produce gentiobiose from amygdalin, one must seek to obtain an enzyme preparation, either from emulsin or from some other source, which hydrolyzes β-glucosides (or in particular Fischer's glucoside) but does not hydrolyze gentiobiose. There is little doubt that the hydrolyses are caused by separate enzymes, since Fischer has shown that amygdalin can be hydrolyzed to a mixture of Fischer's glucoside and glucose by the enzymes of yeast without the occurrence of any hydrolysis of the former substance.

4.[9] TWO ISOMERIC CRYSTALLINE HEXA-ACETATES OF DEXTRO-ALPHA-MANNOHEPTOSE [10]

Fischer and Passmore [11] prepared from *d*-mannose by the cyanohydrin synthesis a sugar, *d*-α-mannoheptose, the configuration of which was established later by Peirce [12] to be



[7] Bromo-acetyl gentiobiose has been prepared in amorphous form by Hudson and Johnson, Jour. Am. Chem. Soc., **39**, 1275; 1917.

[8] Table 29, footnote 1.

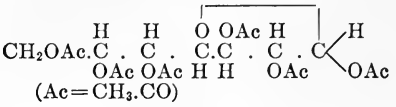
[9] C. S. Hudson and K. P. Monroe, Jour. Am. Chem. Soc., **46**, 979-983; 1924.

[10] This work was done in 1918 in the carbohydrate laboratory of the Bureau of Chemistry, United States Department of Agriculture.

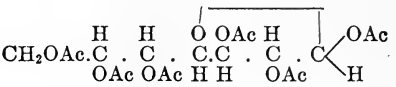
[11] Fischer and Passmore, Ber., **23**, 2226; 1890.

[12] Peirce, Jour. Biol. Chem., **23**, 327; 1915. The proof of the configuration consists in Peirce's demonstration that *d*-α-mannoheptitol is antipodal to *d*-α-galaheptitol and that the same relation holds between the corresponding heptaric acids.

It is to be expected that a sugar of this structure will yield, like glucose, two fully acetylated derivatives of configurations

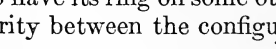


and



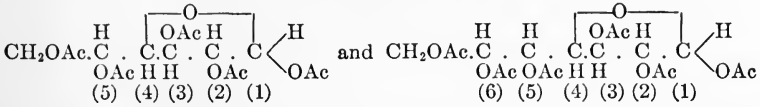
We attempted to prepare these compounds by the usual methods, with the result that we have crystallized two isomeric hexa-acetates and have obtained good evidence of the existence of a third form in an amorphous state. The *first hexa-acetate of d-α-mannoheptose* was prepared by acetylating the sugar with boiling acetic anhydride and sodium acetate. The melting point of the pure crystalline substance is 106° and its rotation in chloroform solution is to the right, $[\alpha]_D^{20} = +24.2°$. When a solution of this hexa-acetate in acetic anhydride containing a small quantity of zinc chloride was warmed on the steam-bath, the specific rotation changed slowly during the course of an hour from an initial value of +22° to a final constant rotation of +80°. This large increase in rotation toward the right indicates that the first hexa-acetate is a β form corresponding, for example, to β-glucose penta-acetate ($[\alpha]_D^{20} = +4°$), and that it changes in large measure in a solution of acetic anhydride and zinc chloride to a more dextrorotatory hexa-acetate, an α form similar, for example, to α-glucose penta-acetate ($[\alpha]_D^{20} = +102°$). This transformation of the first hexa-acetate yielded a sirupy product which crystallized only in small part. The crystals are those of a pure substance which will be designated the *second hexa-acetate of d-α-mannoheptose*, m. p. 139 to 140°, of levorotation $[\alpha]_D^{20} = -31°$ in chloroform. Since the substance rotates to the left it can not be the expected α form. We infer that the strongly dextrorotatory amorphous acetate which constitutes the main portion of the product of the transformation of the first hexa-acetate consists largely of the predicted α form and that the crystalline second hexa-acetate differs in structure from the first in having its internal oxygen ring on some other than the γ carbon atom.

It has been shown [13] that four isomeric crystalline penta-acetates of galactose exist, which may be divided into two pairs, one pair probably possessing the usual γ or butylene ring, while the other pair is presumed to have its ring on some other carbon atom. Because of the close similarity between the configuration of *d*-galactose,



[13] Hudson and Johnson, Jour. Am. Chem. Soc., 38, 1223; 1916.

and that of *d*-α-mannoheptose, which differ solely by the asymmetric carbon atom 6 present in the latter, it is probable that the molecular rotations of corresponding derivatives of the two sugars will be nearly alike. This view may be given quantitative expression as follows. Consider a β-penta-acetate of galactose and a β-hexa-acetate of *d*-α-mannoheptose and assume that both substances are of the butylene ring type. Their structures are



If the molecular rotation of the galactose derivative is P and that of the mannoheptose compound Q, the difference $Q-P$ equals the rotation of the asymmetric carbon atom 6 (or, less probably, atom 5), R_6.

Consider now that the common ring for a similar pair of acetates of the two sugars is on some other carbon atom, for example, carbon 5. The rotation of the new galactose derivative is now P' and that of the new mannoheptose compound Q', but since the two structures still differ only by the presence of asymmetric carbon 6 in one of them, the difference $Q'-P'$ still equals R_6 if the principle of additive optical superposition holds in such cases. Assuming that the principle does hold, it may be expected that a constant difference $Q-P=Q'-P'$ holds between the molecular rotations of derivatives of mannoheptose and those of similar derivatives of galactose, provided the respective derivatives that are compared have like ring structures.

This deduction permits the establishment of a correspondence in ring type between the known acetates of these two sugars as follows: Let it be assumed that the first mannoheptose hexa-acetate is the β form of the butylene ring structure, corresponding to the first penta-acetate of galactose, an assumption which appears justified from the fact that the two substances are produced by the same method in large yield and that each passes in acetic anhydride solution under the catalyzing action of zinc chloride to its more dextrorotatory isomer. Their molecular rotations, $[M]_D$, in chloroform solution are

First *d*-galactose penta-acetate (mol. wt., 390)	$[\alpha]_D^{25°}=+23°$,	$[M]_D^{25°}=+8,970°$
First *d*-α-mannoheptose hexa-acetate (mol. wt., 462)	$[\alpha]_D^{25°}=+24°$,	$[M]_D^{25°}=+11,100°$
	Difference=	$-2,130$

Now the second mannoheptose hexa-acetate can not correspond in configuration to the second galactose penta-acetate because the latter is the α form of the first galactose penta-acetate. Its structure may correspond, however, to that of the third or fourth galactose penta-

acetate. Its molecular rotation in comparison with that of the third galactose penta-acetate is

Third *d*-galactose penta-acetate	$[\alpha]_D^{20} = -42°$,	$[M]_D^{20} = -16,400°$
Second *d*-α-mannoheptose hexa-acetate	$[\alpha]_D^{20} = -31°$,	$[M]_D^{20} = -14,300°$
Difference		$= -2,100°$

It is evident that the difference between these molecular rotations is the same as the difference found in the case of the β forms of the butylene ring structure previously tabulated, a fact which indicates that the third penta-acetate and second hexa-acetate have a like ring structure. Whether the second hexa-acetate can be transformed to an isomer corresponding to the fourth galactose penta-acetate remains to be determined, as our experimental work was interrupted at this point.

The method that is here used to correlate types of ring structure among similar derivatives of different sugars by a comparison of their molecular rotatory powers is probably capable of extensive application. In a later article the method will be extended to a similar comparison of various derivatives of mannose and rhamnose.

(a) EXPERIMENTAL PART

(1) PREPARATION OF THE FIRST HEXA-ACETATE OF *d*-α-MANNOHEPTOSE.—Pure crystalline *d*-α-mannoheptose was acetylated by adding 4 parts of sugar in small portions to 16 parts of acetic anhydride containing 1 part of sodium acetate, at a gentle boil. The solution was poured into water and neutralized with sodium bicarbonate. The acetylated sugar separated as an insoluble phase, sometimes sirupy, sometimes crystallizing immediately after the pouring into water or after the neutralization. In some instances the sirup crystallized only after several days' standing. The crude crystalline product was recrystallized from hot water or 50 per cent alcohol; yield, about 75 per cent of the weight of the sugar. After three recrystallizations from water the melting point and specific rotation became constant; m. p., 106°.

Rotation.—Subs., 0.721, 1.397 in *chloroformum purificatum, U. S. P.* to make 25 cc: rotation, 1.39° and 2.74° to the right, respectively (2 dm tube, sodium light). $[\alpha]_D^{20} = +24.1, +24.4$.

Acetyl determinations were made by boiling the substance with 50 cc of 0.2 *N* sulphuric acid for three hours in a quartz flask with a quartz reflux condenser.

Analyses.—Subs., 0.3234, 0.3167. Calc. for heptose hexa-acetate: acetyl, 55.8. Found: 56.0, 55.7. Subs., 0.0953: CO_2, 0.1698; H_2O, 0.0479. Calc. for heptose hexa-acetate: C, 49.4; H, 5.6. Found: C, 49.7; H, 5.6.

(2) TRANSFORMATION OF THE FIRST AND PREPARATION OF THE SECOND HEXA-ACETATE.—A solution of 10 g of the first hexa-acetate in 100 cc of acetic anhydride containing 2 g of zinc chloride showed a specific rotation of about +22°. When the solution was warmed on the steam-bath for an hour the rotation increased steadily and became constant at about +80°. The solution was then poured into water and neutralized with sodium bicarbonate. The resulting brown, insoluble gum did not crystallize from alcoholic solution but when it was dissolved in ether and the solution allowed to evaporate slowly a low yield, about 10 per cent, of small hard prismatic crystals was obtained. These were recrystallized from ether until the rotation showed a constant value. The melting point of the pure substance was 139 to 140°.

Analyses.—Subs., 0.5036, 0.5373. Found: acetyl, 55.7, 55.9. Subs., 0.1095: CO_2, 0.1975; H_2O, 0.0551. Found: C, 49.2; H, 5.6.

Rotation.—Subs., 0.282 in *chloroformum purificatum, U. S. P.*, to make 25 cc: rotation, 0.70° to the left (2 dm tube, sodium light); $[\alpha]_D^{20} = -31°$.

(b) SUMMARY

The fully acetylated derivatives of *d*-galactose and of *d*-α-mannoheptose appear to correspond in their structures as follows:

Derivatives of *d*-galactose	Corresponding derivatives of *d*-α-mannoheptose	Type of structure [1]
First penta-acetate, m. p., 142°; $[\alpha]_D = +23$	First hexa-acetate, m. p., 106°; $[\alpha]_D = +24$	Both are β forms of probably the butylene ring type.
Second penta-acetate, m. p., 96°; $[\alpha]_D = +107$	Amorphous acetate of high dextrorotation	Probably the α forms of the butylene ring type.
Third penta-acetate, m. p., 98°; $[\alpha]_D = -42°$	Second hexa-acetate, m. p., 139–140°; $[\alpha]_D = -31$	The β forms of some other than the butylene ring type.
Fourth penta-acetate, m. p., 87°; $[\alpha]_D = +61°$	Not yet known	The α forms of this second ring type.

[1] [Note added in 1925.] Recent results from the methylation of β-methyl galactoside and galactonic lactone (Pryde, Jour. Chem. Soc., **123**, 1808; 1923; **125**, 520; 1924; Haworth, Ruell, and Westgarth, ibid., **125**, 2468; 1924) indicate that β-methyl galactoside is of amylene ring structure. Since the chain of β-methyl galactoside has the same rotation as that of galactose and the chain of the tetra-acetate of β-methyl galactoside has the same rotation as that of the first and second galactose penta-acetates it follows that all these substances are of the amylene ring type, and therefore likewise the first hexa-acetate of *d*-α-mannoheptose. The third and fourth galactose penta-acetates and the second *d*-α-mannoheptose hexa-acetate are possibly therefore of butylene ring structure.

5. THE CHLORO- AND BROMO-ACETYL DERIVATIVES OF ARABINOSE. THE NOMENCLATURE OF ALPHA AND BETA FORMS IN THE SUGAR GROUP. SOME DERIVATIVES OF 1,6-DIBROMO-ACETYL GLUCOSE, GENTIOBIOSE, AND MALTOSE [14]

It was shown in article 1 [15] that the values of the specific rotation of chloro- and bromo-acetyl *l*-arabinose in chloroform solution that have been recorded by Chavanne [16] ($[\alpha]_D = -225$ and -283, respectively) are of opposite sign to those predicted by theory ($+231$ and $+264$), and it was stated that "this complete disagreement ob-

[14] C. S. Hudson and F. P. Phelps, Jour. Am. Chem. Soc., **46**, 2591–2604; 1924.

[15] Jour. Am. Chem. Soc., **46**, 466; 1924 (p. 313).

[16] Chavanne, Compt. rend., **134**, 661; 1902.

viously requires further experimental study." We have now prepared these crystalline derivatives by Chavanne's directions from both *l*- and *d*-arabinose and have measured the rotations of the resulting four halogeno-acetyl arabinoses in chloroform solution. From these measurements it appears that Chavanne has mistaken the sign of the rotation of his compounds. The revised rotations are recorded in Table 30.

TABLE 30.—*The rotations of the β-chloro- and β-bromo-acetyl derivatives of arabinose*

Substance	$[\alpha]_D^{20}$ in $CHCl_3$	Molecular rotation $[M]_D$	Rotation of end carbon $A = [M]_D^{20} - B$ [1]
β-Chloro-acetyl *d*-arabinose	−244	−72,000	−41,900 A_{Cl}
β-Chloro-acetyl *l*-arabinose (mol. wt. 295)	+244	+72,000	+41,900 A_{Cl}
β-Bromo-acetyl *d*-arabinose	−288	−97,600	−67,500 A_{Br}
β-Bromo-acetyl *l*-arabinose (mol. wt. 339)	+288	+97,600	+67,500 A_{Br}

[1] The value of B, the rotation of the acetylated basal chain of arabinose, is $B_{l\text{-arabinose}} = +30,100$ from the observed rotations of the alpha and beta forms of *l*-arabinose tetra-acetate (see Article I, p. 313) and consequently $B_{d\text{-arabinose}} = -30,100$.

As these values agree with those calculated in sign and approximately so in magnitude, the exception that was strikingly apparent from Chavanne's data disappears and the halogeno-acetyl derivatives of arabinose fall into line with those of the other sugars by conforming, in first approximation at least, to the Van't Hoff principle of optical superposition.

The observed specific rotations are larger than those that were calculated by the use of the average values $A_{Cl} = 37,800$ and $A_{Br} = 59,300$, from Article 1, Table 24. However, the value of A_{Cl} for chloro-acetyl maltose is 41,400 and for chloro-acetyl glucose is 40,200, which agrees well with the value now found for chloro-acetyl arabinose. The value $A_{Br} = 67,500$ for bromo-acetyl arabinose is considerably larger than those found for this coefficient in Article 1 from the similar derivatives of four other aldoses, the largest previous value being 61,700 for bromo-acetyl xylose. An explanation of this exceptionally large value of A_{Br} for the arabinose derivative is not directly apparent, but there are several facts relating to the question which may here be recorded because they will probably be involved in any solution of the problem. The α and β forms of the tetra-acetate of *l*-arabinose show a difference in molecular rotation of 33,400,[17] a value which is decidedly less than those found for the similar acetates of most other sugars, which range from 36,200 for the xylose tetra-acetates to 40,500 for the maltose octa-acetates. It is to be observed, however, that the mannose penta-acetates differ by only 31,200 and the first and second galactose penta-acetates by 32,700, this last value being quite near that found for the arabinose

tetra-acetates. Hudson and Dale [17] have shown that the observed rotation of β-triacetyl methyl *l*-arabinoside (+182) differs considerably from the calculated value (+197). It has been shown in Article 1 that the observed rotation of the first chloro-acetyl galactose is exceptionally large, and Hudson and Yanovsky [18] have shown that both arabinose and galactose exhibit an anomaly in their mutarotation which distinguishes them from other sugars. Since *d*-galactose and *l*-arabinose are closely similar in configuration, differing only by the interposition of carbon 5 in galactose, it may be that the deviations from the principle of optical superposition that have now been found for certain of their derivatives and the anomaly in their mutarotation are in some manner related to the possession by them of a common type of structure. In any explanation of these peculiarities it should not be overlooked that the existence of four penta-acetates of galactose proves that at least two types of ring structure are to be expected among its derivatives. Possibly similar ring types occur among the derivatives of arabinose.[19]

In article 1 it was shown that the synthesis of Koenigs and Knorr involves a Walden inversion on the asymmetric carbon atom that is concerned in the substitution, α-bromo-acetyl glucose ($[\alpha]_D = +198$) passing by this reaction to β-glucose penta-acetate or β-tetra-acetyl methyl glucoside. No exception to this rule was found among the many cases that were considered. The arabinose derivatives also follow this rule since the molecular rotation of bromo-acetyl *l*-arabinose, +97,600, is more positive than that of the acetylated *l*-arabinose chain, +30,100, while that of the tetra-acetyl *l*-arabinose that results from the bromo derivative by Koenigs and Knorr's synthesis is less positive +13,400 (Hudson and Dale [20]), showing that the rotation of the end asymmetric carbon atom has become reversed in sign during the course of the synthesis.

(a) THE NOMENCLATURE OF ALPHA AND BETA FORMS IN THE SUGAR GROUP

It was shown in article 1 that the numerous aldose halogeno-acyl derivatives therein mentioned are α forms with the exception of the second chloro-acetyl galactose, which was classed as a β compound, though the first chloro-acetyl galactose was shown to be an α form. As the halogeno-acetyl derivatives of arabinose are classed in the present article as β compounds it may appear at first sight that arabinose differs from the other aldoses in the respect that a β deriva-

[17] Hudson and Dale, Jour. Am. Chem. Soc., **40**, 992; 1918.

[18] Hudson and Yanovsky, ibid., **39**, 1013; 1917.

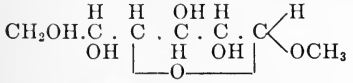
[19] In support of this idea it is recalled that Hudson and Dale (ref. 17) have remarked concerning the large proportion of sirupy arabinose acetate that was obtained along with a small yield of crystalline α-arabinose tetra-acetate from the acetylation of arabinose with acetic anhydride and sodium acetate. This material may represent an arabinose tetra-acetate of new ring structure. The third galactose penta-acetate was discovered in an analogous acetylation of galactose. The subject will be investigated.

[20] Hudson and Dale, Jour. Am. Chem. Soc., **40**, 992; 1918.

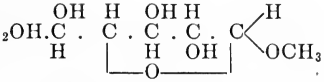
tive rather than an α one is produced when it passes through the usual reactions by which halogeno-acetyl sugars are formed. However, it can be shown that this difference is really only a consequence of the conventional system of nomenclature for α and β forms, and that arabinose resembles the other sugars in typical reactions provided the comparisons are made by the use of the configurations established by Fischer, which is, of course, the logical method. His structure for *l-arabinose* is identical with that for *d-galactose* with the exception of the added presence of carbon 5 in galactose, and as this carbon has little influence on the rotation[21] it is to be expected that structurally similar derivatives of the two sugars will have rotations of similar sign and magnitude. On the other hand, since the sugars belong to opposite (*d* and *l*) series the conventional naming of these structurally similar forms is done by opposed ways; it thus results that β-*l*-arabinose ($[\alpha]_D = +175$, mol. wt. 150) and α-*d*-galactose ($[\alpha]_D = +144$, mol. wt. 180) are the names given to structurally similar forms of these sugars having molecular rotations nearly alike (+26,200 and +25,900). On structural ground, therefore, a β-halogeno-acetyl *l*-arabinose is the analog of an α-halogeno-acetyl *d*-galactose. The reason for naming the forms of the sugars of the dextro and levo series in these opposed ways was explained when the present system of nomenclature was proposed;[22] it follows as a direct consequence of designating the optical antipode of α-methyl *d*-glucoside as α-methyl *l*-glucoside, a designation which Fischer[23] originally applied to these enantiomorphic substances. It further follows logically that the known forms of the halogeno-acetyl derivatives of *l*-arabinose, which are to be designated β compounds on account of their rotations, are to be considered structurally similar to the α forms of the halogeno-acetyl derivatives of *d*-galactose, as mentioned, and that the pentose conforms with the behavior of the hexose in yielding halogeno-acetyl derivatives of this type of structure by the reactions that are customarily employed. In a similar manner the acetylation of *l*-arabinose with acetic anhydride and sodium acetate (Hudson and Dale[24]) yields the α form of the tetra-acetate where *d*-galactose yields its β-penta-acetate, and the reaction between *l*-arabinose and acidified methyl alcohol yields β-methyl *l*-arabinoside where *d*-galactose yields α-methyl *d*-galactoside; in these cases again the difference is only an apparent one due to a convention of nomenclature and when the comparison is made on structural grounds the two sugars of similar structure react alike. It seems important to emphasize these matters in order to prevent the drawing of erroneous conclusions when the differences of reactivity of the α and β forms

[21] Hudson, Jour. Am. Chem. Soc., **33**, 409; 1911.
[22] Hudson, ibid., **31**, 66; 1909.
[23] Fischer, Ber., **28**, 1145; 1895. See also Fischer and Armstrong, Ber., **34**, 2887; 1901, footnote 3.
[24] Hudson and Dale, Jour. Am. Chem. Soc. **40**, 992; 1918.

of the various sugars and their derivatives are compared, an interesting experimental study which has already received considerable attention[25] and will doubtless be greatly extended. An example may serve to illustrate the pitfalls that may be expected in such studies unless the necessary caution concerning nomenclature is used. From a comparison of the configurations of *d*-glucose and *l*-idose (Rosanoff's nomenclature) it is evident that the hypothetical β-methyl *l*-idoside is the structural relative of α-methyl *d*-glucoside rather than of β-methyl *d*-glucoside.[26] The configurations of the two compounds are to be written.



α-Methyl *d*-glucoside, I



β-Methyl *l*-idoside, II

On account of the close similarity between the structures of these substances there is a possibility that the enzyme α-glucosidase may hydrolyze the idoside and if such prove to be the case it might possibly be inferred that an α enzyme hydrolyzes a derivative belonging in the β series. Such a conclusion would be incorrect because the idoside is not a structural relative of β-methyl glucoside.

Svanberg and Josephson[27] have recently criticized the customary naming of α and β forms on the basis of comparative rotations with the general statement that this system is of "hypothetical character" and have suggested that a comparison of the chemical or biochemical reactivities of the two forms of a given sugar furnishes a preferable basis of nomenclature.

The ambiguities and exceptions which one meets at the present time in trying to found such a new system are well illustrated, however, by several of the experimental facts which they record and are further emphasized by the difficulty which Freudenberg and Doser[28] have mentioned in the case of di-acetone glucose, where one can not decide whether the greater reactivity of β- over α-glucose in combining with acidified acetone should be referred to a faster rate of reaction in a homogeneous system or to the greater solubility of β-glucose in the solvent. A requirement of a satisfactory system of nomenclature is that it shall not lead to ambiguity, and it does seem that the system now in use meets this demand; the precision with which classifications can be made under it is well shown in the articles of this series. It is true that it is founded upon a theoretical basis, which is Van't Hoff's principle of optical superposition, but the applicability of this principle to a large number of substances of the sugar

[25] Compare Svanberg and Josephson, Ber., **57B**, 297; 1924.

[26] In naming the forms of methyl *l*-idoside, which as yet have not been prepared, the more dextrorotatory one is to be designated β because the sugar belongs in the *levo* series, but the rotation of this form will in all probability, on account of the similarity of structure between *d*-glucose and *l*-idose, and the small rotation of carbon 5, be found to be very near that of α-methyl *d*-glucoside.

[27] Loc. cit.

[28] Freudenberg and Doser, Ber., **56B**, 1246; 1923.

group has been firmly established by many experimental investigations during the past 15 years. The numerical relations which have been found among the rotations of the sugars and their derivatives are not hypotheses, but are facts obtained from physical measurements of rotations, and the theory which so simply and clearly accounts for the signs and magnitudes of these rotations is the one upon which the present system of naming the α and β forms is founded. It seems very desirable that any system of nomenclature in the sugar group should have this kind of theoretical foundation. One recalls in this connection that the facts from which the configurations of the sugars were established by Fischer prove these configurations only because they can be directly deduced from a theory, namely, the Van't Hoff-LeBel hypothesis of an asymmetric carbon atom of definitely assumed characteristics.[29] To attempt the replacement of the present system of naming α and β forms by any plan which bases its distinctions upon vaguely definable conceptions of relative chemical or biochemical reactivity seems a step backward. The ascertainment of these relative reactivities is a useful study of the dependence of reactivity upon structure, but the matter of a logical system of nomenclature is a separate subject.

In connection with this topic reference may be made to the recent article by R. Kuhn[30] in which he proposes to classify glucosides on the basis of an experimental identification of the form of the parent sugar that is liberated when the glucoside is hydrolyzed by an enzyme. He would base the classification upon the rotatory power, the comparison of "other physical constants," or upon empirical rules of synthesis, only when the method of enzymotic hydrolysis can not be applied. It does not seem warranted to place the deductions that can be drawn from the comparison of rotatory powers in the sugar group as of no greater value than the uncertain conclusions that are at times obtained from comparisons of melting points, refractive indices, heats of combustion, etc., or even the conclusions that are derived from rules of synthesis, though it is not to be denied that these last are often of considerable importance as indications, as has frequently been emphasized in the articles of this series in the case of the rule for Koenigs and Knorr's reaction. The large difference between the rotations of the members of an α-β pair of compounds in the sugar group is dependent upon the oppositely directed rotations of a single carbon atom (carbon 1 of the aldoses) and it is the opposed form of the arrangement in space of the groups attached to

[29] The matter can not be expressed more clearly than by Fischer's introductory sentence in the immortal article that records the proof of the configuration of glucose and originates a theoretical chemistry of the sugars [Ber., **24**, 1836; 1891]: "Alle bisherigen Beobachtungen in der Zuckergruppe stehen mit der Theorie des asymmetrischen Kohlenstoffatoms in so vollkommener Uebereinstimmung, dass man schon jetzt den Versuch wagen darf, dieselbe als Grundlage für die Klassification dieser Substanzen zu benutzen."

[30] Kuhn, Ber., **56B**, 857; 1923.

this same carbon that makes possible the existence of two isomers in place of a single substance. There is here, accordingly, a simple relationship between the two space-structures of this determinative or "key" carbon atom present in the isomers and the difference between their rotations, and this relationship is not confused by the influence of secondary factors, as may probably be the case when structures are inferred from the relative values of other physical constants.[31] Although E. F. Armstrong's method of enzymotic hydrolysis has been of much importance in showing the relationship of a few glucosides to definite forms of their parent sugars, its applicability is so limited on account of the specific nature of enzyme actions that its main value lies in its occasional use as a control upon the classifications that can nearly always be readily made on the basis of rotatory powers. Moreover, while such hydrolyses can at times show the existence of common structural features in a glucoside and one form of its parent sugar they fail when an attempt is made to extend the comparisons to show correlations of structure among the glucosidic derivatives of different sugars. On the other hand, the comparison of rotatory powers gives important evidence on this question, as was shown in article 4 for the members of the complicated group of acetates of galactose and α-mannoheptose.

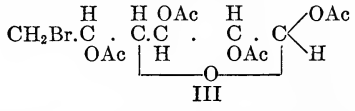
The present system of naming α and β forms on the basis of rotatory powers is so definite in its classifications, the experimental determinations which are required for its application (measurements of rotation) are so readily made, and such important information regarding structural types in the sugar group is disclosed by it, that it seems most advisable to continue its use. It should be borne in mind, however, that since the system is founded in part upon the dextro and levo classification of the sugars that Fischer introduced, its classifications are arbitrary in the same sense as are those of Fischer, and at times they are at first sight somewhat confusing, as in the case where an α form of one sugar is evidently of closer structural relationship to a β form of another sugar than to its α form.

(b) THE CALCULATED ROTATIONS OF FISCHER AND ARMSTRONG'S DIBROMO-ACETYL GLUCOSE (1,6-DIBROMO-2,3,5-TRI-ACETYL ALPHA-GLUCOSE), ITS BETA-METHYL GLUCOSIDE (6-BROMO-2,3,5-TRI-ACETYL BETA-METHYL GLUCOSIDE), AND ALPHA-TETRA-ACETATE (6-BROMO-1,2,3,5-TETRA-ACETYL ALPHA-GLUCOSE)

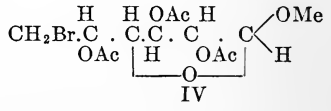
In article 1 the specific rotation of the first of these compounds, which has the structural formula XVI (p. 320), was calculated from the rotations of two benzyl glucosides that are related to it to be

[31] It seems very probable that the position of the ring in a sugar or its derivatives may eventually become an important consideration in the classification of α and β forms and it may be advisable from theoretical considerations of the space relationship of asymmetric carbon 1 to different types of ring structure to reverse in a few instances the present names, but such possible changes would constitute a development of the present system of nomenclature by the addition of new theoretical ideas, not its abandonment, and the need for such changes can only be determined after the ring structures are more definitely known than at present

+169. This result is in error, however, because the molecular weight of dibromo-acetyl glucose was taken as 474. The correct weight is 432 and consequently the calculated rotation becomes +186 in place of +169. In the calculation there is the uncertainty that the rotation of one of the benzyl glucosides was measured in alcohol rather than in chloroform. There has now been found an independent way by which this calculation can be made. Fischer, Helferich, and Ostmann [32] have observed the specific rotation of 6-bromo-1,2,3,5-tetra-acetyl β-glucose (mol. wt., 411) to be +12.1 in acetylene tetrachloride; hence its molecular rotation is (12.1) (411) = +4,970. The structure of the substance, which is considered to be a β form because it is derived from dibromo-acetyl glucose by Koenigs and Knorr's synthesis, is III, and accordingly its molecular rotation is to be written $B'_{glucose} - A_{Ac} = +4,970$. Since $A_{Ac} = +19,100$ [Article I, p. 317] the rotation of the basal chain is $B'_{glucose} = +24,100$. This is an important determination because from it there can be calculated by the addition or subtraction of the known values of A_{Me}, A_{Ac}, etc., the rotations of many 6-bromo substitution products derived from glucose and from many other sugars. The specific rotation of dibromo-acetyl glucose becomes thus $[\alpha]_D = (B'_{glucose} + A_{Br}) \div$ mol. wt. $= (24,100 + 59,300) \div 432 = 193$ in chloroform. The two calculated values for this substance, 186 and 193, agree fairly well. The latter one seems more reliable because the measurements from which it is derived were made throughout in chloroform or acetylene tetrachloride solution.[33]



III



IV

[32] Fischer, Helferich, and Ostmann, Ber., **53**, 873; 1920.

[33] This example illustrates the importance attached to the selection of a solvent in the measurement of the rotations of new compounds. When Hudson and Dale [Jour. Am. Chem. Soc., **37**, 1264; 1915] determined the coefficients $B_{glucose}$, A_{Ac} and A_{Me}, they measured the rotations of the glucose penta-acetates and methyl glucoside tetra-acetates in six solvents to learn which one was best suited for general use in testing the applicability of the principle of optical superposition. Benzene was shown to be quite unsuitable, methyl alcohol and acetic acid somewhat unsatisfactory, while chloroform and ethyl alcohol (absolute) gave good results. Chloroform was selected for the subsequent measurements of many acetylated derivatives of the sugars, from which the coefficients now in use have been derived, on account of the fact that it is an excellent general solvent and that the rotations in the literature pertaining to sugar derivatives that are insoluble in water refer in the majority of cases to their chloroform solutions. Unfortunately, the sugars and some of their derivatives are not soluble in chloroform; water has accordingly been used as the solvent for these substances with good results, as it appears that optical superposition holds fairly closely for both aqueous and chloroform solutions of many substances belonging in the sugar group. A more precise study of the question of the solvents suitable for such studies and also a comparison of the rotations for light of various wave lengths would be very useful. Until better recommendations can be made, rotations should be compared in water or in chloroform solution wherever possible. A large number of compounds which were prepared in Fischer's laboratory during the later years of his life were measured in acetylene tetrachloride solutions. Fortunately this solvent appears to give values almost identical with those of chloroform solutions, doubtless on account of the close chemical relationship of the two liquids, but even so it would seem advisable in future research work to discard the use of acetylene tetrachloride or preferably to measure the rotations in chloroform as well. It is to be hoped that investigators who have rare sugar derivatives in hand may measure the rotations in chloroform where the solubility is sufficient, as an aid to the development of such studies as are being described in the present series of articles.

Brigl and Wrede [34] have reported the preparation of a substance which is probably the α form of 6-bromo-1,2,3,5-tetra-acetyl glucose (that is, the α form corresponding to the β derivative that is represented by III), but there appears to be no record so far of its rotation. The value obtained by calculation is $(B'_{glucose} + A_{Ac}) \div 411 = 105$.

Fischer, Helferich, and Ostmann [35] have prepared 6-bromo-2,3,5-tri-acetyl β-methyl glucoside (mol. wt. 383, Structure IV), but its rotation was not recorded. The calculated value is $[\alpha]_D = (B'_{glucose} - A_{Me}) \div 383 = (24{,}100 - 26{,}900)$[36] $\div 383 = -7$ in chloroform.[37]

(c) THE ROTATION OF ALPHA-BROMO-ACETYL GENTIOBIOSE OBSERVED BY ZEMPLÉN

The specific rotation of this substance was calculated in article 1 to be +108 in chloroform. Zemplén [38] has recently succeeded in preparing the compound in crystalline form and has found the value $[\alpha]_D^{19} = +112$ in chloroform, which agrees well with the predicted rotation. As the calculation was based on the assumption that the substance belongs in the α series, this allocation may now be considered established. Since this α derivative has been found [39] to yield β-methyl gentiobioside hepta-acetate by Koenigs and Knorr's synthesis, it is evident that the usual Walden inversion here takes place. The value of $B_{gentiobiose}$ has been found to be +15,900 from the rotations of the two forms of gentiobiose octa-acetate [Art. I, p. 323]. The molecular rotation of α-bromo-acetyl gentiobiose is $(112)(699) = +78{,}300 = (B_{gentiobiose} + A_{Br})$; hence $A_{Br} = +62{,}400$, which agrees with the values of this coefficient found previously. This confirmation of theory by Zemplén's recent measurement lends strong support to the assumptions upon which the calculations have been based, as do likewise the newly measured rotations of the halogeno-acetyl derivatives of arabinose, and the recent proof by Haworth and Wylam that the biose of amygdalin is gentiobiose, a conclusion that was reached in article 3 from data on rotatory powers.[40]

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[34] Brigl and Wrede, Z. physiol. Chem., **116**, 13; 1921.

[35] Fischer, Helferich, and Ostmann, Ber., **53**, 873; 1920.

[36] The value of A_{Me} is taken from Article I, p. 316.

[37] Since the publication of these calculations Dr. F. Wrede has kindly informed the writer that he had measured previously (Z. physiol. Chem., **115**, 284; 1921) the rotations in ethyl acetate of the three substances here discussed. He has now communicated by letter his recent measurements of the rotations of two of them in chloroform. His values are: 1,6-dibromo-tri-acetyl-glucose, $[\alpha]_D^{14} = +184.1$ in ethyl acetate; 6-bromo-2,3,5-tri-acetyl β-methyl glucoside, $[\alpha]_D^{20} = -7.78$ in ethyl acetate, -2.9 in chloroform; 6-bromo-1,2,3,5-tetra-acetyl α-glucose, $[\alpha]_D^{14} = +109.0$ in ethyl acetate, $+102.6$ in chloroform. Karrer and Smirnoff (Helv. chim. acta, **5**, 128; 1922) also record $[\alpha]_D = +189.2$ and $+191.4$ for 1,6-dibromo-acetyl glucose in chloroform. Irvine and Oldham (J. Chem. Soc., **127**, 2729; 1925) have recently found $[\alpha]_D = +189.9$ for this substance in chloroform and -1.4 for 6-bromo-2, 3, 5-tri-acetyl β-methyl glucoside. The calculated values agree well with these observations.

[38] Zemplén, Ber. **57B**, 698; 1924.

[39] Hudson and Johnson, Jour. Am. Chem. Soc., **39**, 1272; 1917.

[40] The article by Haworth and Wylam [Jour. Chem. Soc., **123**, 3120; 1923] was received for publication Nov. 3, 1923, and Article 3 of this series Nov. 14, 1923. These independently conducted researches have led to the same conclusion, as regards the identity of the biose of amygdalin with gentiobiose, by quite different methods of study.

(d) THE CALCULATED ROTATIONS OF SOME ACYL DERIVATIVES OF MALTOSE AND GENTIOBIOSE

On account of the recent demonstration that maltose and gentiobiose constitute the first known α-β pair of compound sugars (Haworth and Wylam, Hudson) the comparison of the various properties of these sugars and their derivatives becomes a subject of interest. As a beginning in this field there are recorded in Table 31 the calculated rotatory powers in chloroform solution of a number of their acyl derivatives. The method that is followed in the calculations has been illustrated so often that a tabulation of the data may here suffice. The values of the various coefficients used in the calcula-

TABLE 31.—*The rotations of some acyl derivatives of maltose and gentiobiose*

Substance	Molecular weight	Calculated molecular rotation	$[\alpha]_D$ In chloroform	
			Calculated	Observed
α-Fluoro-acetyl maltose	638	$B_{maltose} + A_F = 62{,}700 + 9{,}800$	114	?
α-Chloro-acetyl maltose	655	$B_{maltose} + A_{Cl} = 62{,}700 + 37{,}900$	154	[1] 159
α-Bromo-acetyl maltose	699	$B_{maltose} + A_{Br} = 62{,}700 + 59{,}300$	175	[2] ?
α-Iodo-acetyl maltose	746	$B_{maltose} + A_I = 62{,}700 + 85{,}400$	199	?
α-Nitro-acetyl maltose	681	$B_{maltose} + A_{NO_3} = 62{,}700 + 37{,}100$	147	[1] 149
β-Hepta-acetyl methyl maltoside	650	$B_{maltose} - A_{Me} = 62{,}700 - 26{,}900$	55	[3] 54
α-Fluoro-acetyl gentiobiose	638	$B_{gentiobiose} + A_F = 15{,}900 + 9{,}800$	40	?
α-Chloro-acetyl gentiobiose	655	$B_{gentiobiose} + A_{Cl} = 15{,}900 + 37{,}900$	82	?
α-Bromo-acetyl gentiobiose	699	$B_{gentiobiose} + A_{Br} = 15{,}900 + 59{,}300$	108	[4] 112
α-Iodo-acetyl gentiobiose	746	$B_{gentiobiose} + A_I = 15{,}900 + 85{,}400$	136	?
α-Nitro-acetyl gentiobiose	681	$B_{gentiobiose} + A_{NO_3} = 15{,}900 + 37{,}900$	78	?
β-Hepta-acetyl methyl gentiobioside.	650	$B_{gentiobiose} - A_{Me} = 15{,}900 - 26{,}900$	−17	[5] −19

[1] From article 1.
[2] Bromo-acetyl maltose was crystallized by Fischer and Armstrong [Ber., **35**, 3153; 1902], but they did not measure its rotation.
[3] Hudson and Sayre, Jour. Am. Chem. Soc., **38**, 1867; 1916.
[4] Zemplén, Ber., **57B**, 698; 1924.
[5] Hudson and Johnson, Jour. Am. Chem. Soc., **39**, 1272; 1917.

tions are taken from article 1, A_{Cl} being corrected as mentioned. The uniformly good agreement between the observed and the calculated rotations of the five compounds that have already been investigated seems a reliable indication that the calculated rotations of the remaining substances are near the true values.[41]

(e) POSTSCRIPT

After the manuscript of the present article was completed, a publication by D. H. Brauns [42] has appeared in which the rotations in chloroform solution of fluoro, chloro, bromo, and iodo acetyl *l*-arabi-

[41] In connection with the subject of the related structures of maltose and gentiobiose attention is called to the fact that the rates of mutarotation of these sugars that are recorded in the literature are closely the same. When it was shown from rotatory data that lactose and cellobiose possess the same linkage between their respective hexose constituents [Hudson, Jour. Am. Chem. Soc., **38**, 1573; 1916], which was subsequently proved by Haworth and his coworkers to be the 1-5 union, it was mentioned that the rates of mutarotation of lactose and cellobiose have practically identical values. These facts, taken in conjunction with some unpublished comparisons of a similar nature, indicate that the comparative rates of mutarotation of substances of the sugar group can be correlated quite directly with structures. This will be further developed in a subsequent article, and in particular the rates of mutarotation of glucosamine and chondrosamine will be used to throw light on their structures, which are at present not definitely known.
[42] Jour. Am. Chem. Soc., **46**, 1484; 1924.

nose are recorded. Brauns has corrected the sign of the rotation of Chavanne's two compounds, but has evidently not read the remarks on that subject that were published in article 1 of this series [p. 313], as he does not refer to that previous indication of the error in Chavanne's signs. Our values for the rotations of chloro and bromo acetyl *l*-arabinose agree closely with those of Brauns and there can be no longer any doubt regarding the correct signs. It may be added that our experimental work was performed in the latter months of 1923 and that we had no knowledge that Brauns was measuring the same compounds. It seems well worth while that there should have been this partial duplication of work because of the theoretical importance attached to the correction of Chavanne's signs. The rotations found by Brauns are here tabulated in the usual manner to show the values of the coefficients that may be derived from the molecular rotations.

TABLE 32.—*The rotations of the halogeno-acetyl derivatives of l-arabinose (Brauns' measurements)*

Substance	Molecular weight	$[\alpha]_D^{20}$ in $CHCl_3$	Molecular rotation $[M]_D$	Rotation of end carbon $A = [M]_D - B_{l\text{-arabinose}}$
β-Fluoro-acetyl *l*-arabinose	278	+138	38,400	8,300 (A_F)
β-Chloro-acetyl *l*-arabinose	295	+244	72,000	41,900 (A_{Cl})
β-Bromo-acetyl *l*-arabinose	339	+287	97,300	67,200 (A_{Br})
β-Iodo-acetyl *l*-arabinose	386	+339	130,800	100,700 (A_I)

The very large difference between A_I for iodo-acetyl arabinose and iodo-acetyl glucose (from article 1, Table 24), 100,700 − 85,600 = 15,100, corresponding to about 36° in their specific rotations, seems to be evidence of considerable weight that there is a difference between the ring structures of the substances, which supports the similar view that has been suggested earlier in this article on account of the rather large rotation of bromo-acetyl arabinose. The value of A_F is not appreciably different from that obtained from fluoro-acetyl xylose (8,400) in article 1. The four halogeno-acetyl derivatives of arabinose are to be classed as β compounds on the basis of their rotations for the reasons mentioned earlier in the present article.[43]

[43] It was mentioned in article 1 (p. 322) that "the values for the rotations of the terminal asymmetric carbon atom now known for so many types of derivatives allow the calculation of the rotations of a large number of halogeno-acyl, nitro-acyl, and mixed acyl derivatives of various sugars and glucosides," and that "it does not seem desirable to burden the literature with these calculated values, as the typical examples which have been given will illustrate the method of applying the appropriate coefficients in particular cases." The fluoro- and iodo-acetyl derivatives of arabinose are such cases and since Brauns has not referred to the values that may be so calculated they are here recorded from the data of article 1.

Fluoro-acetyl *l*-arabinose, $[\alpha]_D = (B_{l\text{-arabinose}} + A_F) \div$ mol. wt. $= (30{,}100 + 9{,}800) \div 278 = +144$

Iodo-acetyl *l*-arabinose, $[\alpha]_D = (B_{l\text{-arabinose}} + A_I) \div$ mol. wt. $= (30{,}100 + 85{,}400) \div 386 = +299$

The calculated and observed values for the fluoro derivatives agree fairly well and, as indicated previously, the agreement is almost exact if the value of A_F from fluoro-acetyl xylose is used in the calculation. The calculated value for the iodo compound is much lower than the observed, a fact which may prove to be of much theoretical importance, as has been mentioned.

(f) EXPERIMENTAL PART

(1) PREPARATION OF CHLORO-ACETYL *d*-ARABINOSE.—The directions of Chavanne were followed. Five g of levo-rotatory *d*-arabinose ($[\alpha]^{20}_{D} = -105$) was dissolved in 10.5 g of acetyl chloride by shaking the mixture in a machine during about 14 hours, using a flask fitted with a calcium chloride outlet tube. The resulting solution was taken up with dry chloroform, washed first with ice water containing a little sodium bisulphite, then with ice water made slightly alkaline with sodium carbonate, and then with ice water alone. The chloroform solution was dried with sodium sulphate and diluted with petroleum ether. On evaporation in a current of dry air crystallization took place. The crystals were washed with dry ether, recrystallized from benzene, again washed with ether and dried in a desiccator over sulphuric acid and potassium hydroxide to constant weight. The $[\alpha]^{20}_{D}$ value in chloroform solution was -227. These crystals were recrystallized from chloroform solution by the addition of ether and the substance then showed $[\alpha]^{20}_{D} = -245$ and two subsequent recrystallizations gave products with rotations of -242 and -246, respectively. The average value $[\alpha]^{20}_{D} = -244$ is taken to be the specific rotation of chloro-acetyl *d*-arabinose in chloroform solution. An estimation of chlorine by dissolving the substance in dilute nitric acid and titrating according to the Volhard method showed the theoretical value for chloro-triacetyl arabinose.

(2) PREPARATION OF CHLORO-ACETYL *l*-ARABINOSE.—Starting with dextro-rotatory *l*-arabinose and acetyl chloride, chloro-acetyl *l*-arabinose was prepared similarly. The values for the recrystallized substance obtained in two experiments were $[\alpha]^{20}_{D} = +243.1$ and $+243.7$ in chloroform.

(3) PREPARATION OF BROMO-ACETYL *d*-ARABINOSE.—This was readily prepared from levo-rotatory *d*-arabinose and acetyl bromide by interaction at zero in an ice bath. The crystals were recrystallized from chloroform by adding ether and the first crop showed $[\alpha]^{20}_{D} = -284$. After several recrystallizations a constant value of -290 in chloroform was found. A bromine estimation by the Volhard method gave the theoretical value for bromo-triacetyl arabinose.

(4) PREPARATION OF BROMO-ACETYL *l*-ARABINOSE.—This was prepared similarly from dextro-rotatory *l*-arabinose and acetyl bromide and recrystallized several times. The values found were $[\alpha]^{20}_{D} = -287$ and -285. The average value 288 is selected as the magnitude of the rotation of both forms of bromo-acetyl arabinose. In all the measurements the readings were made in a Bates type saccharimeter with white light and a dichromate filter, which gives a light of effective wave length about 585 instead of the 589 sodium line; in consequence the values may be one or two degrees too large. The rotatory dispersion of the solutions is enough different from that

of quartz to make the setting somewhat uncertain and it is probably for this reason that the agreement between the values of the rotations of the dextro and levo forms of bromo-acetyl arabinose is not better. However, a precision measurement of the rotations has not been the object of the present investigation. The results recorded in the table are probably correct within 2°.

The four halogeno-acetyl derivatives appear to be quite stable if kept dry, even when exposed to diffused sunlight. They have been kept for months at room temperature in a desiccator over sulphuric acid and potassium hydroxide, and in some cases over potassium hydroxide alone, without apparent deterioration. They form relatively large, perfect and colorless crystals when grown slowly from solution.

(g) SUMMARY

An experimental revision of the rotations of the chloro and bromo acetyl derivatives of arabinose confirms the calculations made in article 1, as it is shown that the correct signs are the reverse of those previously recorded by Chavanne. In the meantime D. H. Brauns has confirmed this deduction from theory through his preparation and measurement of the rotations of fluoro, chloro, bromo, and iodo acetyl *l*-arabinose. The rotation of fluoro-acetyl arabinose agrees well with the calculated value. Iodo-acetyl arabinose exhibits a rotation about 36° larger than that calculated by the use of the coefficient A_I derived from the rotation of iodo-acetyl glucose and it is suggested that this large difference may indicate the presence of a new ring type of structure in the arabinose compound. This indication is supported by the rather large rotation of bromo-acetyl arabinose. The rotation of chloro-acetyl arabinose is somewhat, but not considerably, larger than the calculated value. On the basis of rotatory powers it is shown that the known halogeno-acetyl arabinoses, which have hitherto not been classified, are to be named β compounds. It is emphasized that the synthesis of Koenigs and Knorr involves a Walden inversion on the end asymmetric carbon atom in all cases now known. A discussion of the nomenclature of α and β forms in the sugar group brings out the importance of following the system of nomenclature that one of us suggested in 1909, now in general use; a number of arguments are presented which lead us to reject the recent suggestions of Svanberg and Josephson and of Kuhn, who have favored the substitution of other methods of naming. The specific rotation of α-bromo-acetyl gentiobiose calculated in article 1, +108, has now been verified through Zemplén's recent preparation of this substance; he records the value +112. The conclusions of article 3, based upon rotations, that the biose of amygdalin is gentiobiose and that gentiobiose and maltose constitute the first known α-β pair of compound sugars, have been proved inde-

pendently by Haworth and Wylam through conventional methods, as described in their article published concurrently with article 3. Calculations are recorded of the rotations of 1,6-dibromo-2,3,5-tri-acetyl α-glucose and the related 6-bromo-1,2,3,5-tetra-acetyl α-glucose and 6-bromo-2,3,5-tri-acetyl β-methyl glucoside; these substances have been described in the literature without records of their rotations. From the recorded rotation of 6-bromo-1,2,3,5-tetra-acetyl β-glucose the value of the coefficient $B'_{glucose} = +24{,}100$ has been found. It is shown that the calculated and observed rotations of five acyl derivatives of gentiobiose and maltose agree closely; the rotations of seven related derivatives have now been calculated (Table 31). Arguments are presented in support of the recommendation that measurement of the rotations of new optically-active compounds, particularly those of the sugar group, be made in water or in chloroform solution wherever possible.

6. THE ROTATORY POWERS OF THE ALPHA AND BETA FORMS OF METHYL *d*-XYLOSIDE AND OF METHYL *l*-ARABINOSIDE [44, 45]

The rotatory powers of the α and β forms of methyl *d*-glucoside and of methyl *d*-galactoside are known with precision from the careful reinvestigation of these substances by E. Bourquelot.[46] The present investigation was undertaken with the purpose of determining accurately the rotations of the α and β forms of methyl *d*-xyloside and of methyl *l*-arabinoside as a supplement to Bourquelot's data so that the rotations of these four isomeric pairs of methyl glycosides of the four aldoses may be used for a more exact quantitative study of the relation between rotatory power and structure than has been possible in the past.[47] The principal problem in the obtaining of accurate data respecting such compounds is the purification of the substances themselves and particularly the thorough separation of isomeric forms by crystallization from suitable solvents.

The two forms of methyl xyloside and one of the forms of methyl arabinoside were discovered by Emil Fischer.[48] The present results agree with his values of the rotations of the methyl xylosides within about 0.5 per cent. He did not record the rotation of the arabinoside. The second form of methyl arabinoside was discovered by Purdie and Rose,[49] who measured not only its rotation but the rotation of the first form as well. The present results closely confirm their value of the rotation of the first, or Fischer's arabinoside, but give a greatly different value from theirs in the case of the second arabino-

[44] This work was done in 1917 in the carbohydrate laboratory, Bureau of Chemistry, U. S. Department of Agriculture.

[45] C. S. Hudson, Jour. Am. Chem. Soc., **47**, 265-268; 1925.

[46] Bourquelot, Ann. chim., **7**, 219; 1917.

[47] Hudson, Jour. Am. Chem. Soc., **31**, 66; 1909.

[48] Fischer, Ber., **28**, 1145; 1895.

[49] Purdie and Rose, Jour. Chem. Soc., **89**, 1204; 1906.

side ($[\alpha]_D^{20} = +17.3$ in place of $+73$). The difference is probably due to the presence of some of the first arabinoside in their compound, which is readily accounted for by the great difficulty of separating the two isomers, especially when only small quantities of material are subjected to purification. The new set of values of the rotations is used in the accompanying article (article 7) in a comparison of the rotatory powers of nearly all the known methyl glycosidic derivatives of the various sugars.

The directions for preparing the methyl xylosides and methyl arabinosides specified in the present article are based upon many experiments undertaken to ascertain the best conditions for applying to xylose and arabinose Bourquelot's modification [50] of Fischer's method [51] for preparing methyl glucoside. By this method of preparation the use of sealed tubes or an autoclave is avoided and the combination of the sugar with the methyl alcohol is effected simply by boiling the slightly acidified solution for a few hours.

(a) PREPARATION OF THE ALPHA AND BETA FORMS OF METHYL *d*-XYLOSIDE

(1) β-METHYL *d*-XYLOSIDE.—Bourquelot has shown that methyl glucoside may be prepared by boiling a solution of glucose in methyl alcohol containing 0.25 per cent of hydrochloric acid, a method that offers advantage over the directions of Fischer which require the heating of the solution at 100° in an autoclave or a sealed tube. After trying several strengths of acid and various times of boiling, we adopted the following directions for preparing the methyl xylosides by Bourquelot's procedure. One hundred g of dextrorotatory *d*-xylose ($[\alpha]_D^{20} = +18$) was boiled with 1 liter of pure anhydrous methyl alcohol containing 1 per cent of dry hydrogen chloride on the steam bath under a reflux condenser during six hours. A few pieces of porous plate insured steady boiling. The acid was then neutralized with silver carbonate and the solution was filtered, decolorized with active carbon, filtered again and concentrated to a thick sirup under reduced pressure. By treating the sirup with ethyl acetate 42 g of crystalline β-methyl *d*-xyloside was obtained. The mother liquor was used for the preparation of the isomeric α-form, as will be described. The crystals of the β-xyloside were purified by recrystallization from absolute alcohol. After one recrystallization, $[\alpha]_D^{20} = -65.6$ in aqueous solution (2.520 g of substance, 25 cc of solution, reading 6.61° to the left, in a 1-dm tube), and after a second recrystallization from absolute alcohol $[\alpha]_D^{20} = -65.5$, (3.430 g of substance, 25 cc of solution, reading 8.95° to the left in a 1-dm tube). The melting point of the twice recrystallized substance was 157°. The corresponding values of Fischer are −65.8 and 157°.

[50] Bourquelot, Ann. chim., 3, 298; 1915. [51] Fischer, Ber., 28, 1145; 1895.

(2) α-METHYL *d*-XYLOSIDE.—The mother liquor of the initial crystallization of the β-xyloside from ethyl acetate was placed in a vacuum desiccator and occasionally stirred. In the course of several weeks it became a semisolid crystalline mass. The sirupy portion was thinned with a small amount of methylethyl ketone and the crystals of α-methyl *d*-xyloside were then separated by pressing the mass between several thicknesses of filter paper. After two recrystallizations from methylethyl ketone, $[\alpha]_D^{20} = +152.8$; after another, the value was +153.7; and after a fourth it was +153.9, (10.556 g of substance, 100 cc of aqueous solution, reading 32.50° to the right, in a 2-dm tube). Fischer found +153.2. The use of methylethyl ketone in place of the ethyl acetate that Fischer employed is of much advantage in the purification of α-methyl xyloside.

(b) PREPARATION OF THE ALPHA AND BETA FORMS OF METHYL *l*-ARABINOSIDE

(1) β-METHYL *l*-ARABINOSIDE.—After trials with various percentages of acid and times of boiling, the following directions were adopted for preparing the two forms of methyl *l*-arabinoside. One hundred g of dextro-rotatory *l*-arabinose ($[\alpha]_D^{20} = +104$ to +105) was boiled with 1 liter of pure anhydrous methyl alcohol containing 1.5 per cent of dry hydrogen chloride on the steam bath under a reflux condenser during three hours. The acid was neutralized with silver carbonate and the solution filtered, decolorized with active carbon, and filtered again. On boiling down the solution under reduced pressure, β-methyl *l*-arabinoside crystallized and the crystals were filtered off; yield, 30 g. These crystals were extracted with boiling ethyl acetate to remove as much sirupy impurity as possible and were then recrystallized from absolute alcohol. The product from this first recrystallization gave $[\alpha]_D^{20} +243.1$. After repeating the extraction with ethyl acetate and the crystallization from absolute alcohol the value of $[\alpha]_D^{20}$ rose to +245.6, but a third extraction and recrystallization gave crystals of the same rotation, $[\alpha]_D^{20} = +245.5$ (1.813 g of substance, 25 cc of aqueous solution, reading 33.60° to the right in a 1-dm tube), which is taken as the specific rotation of pure β-methyl *l*-arabinoside. The melting point was 169°. Purdie and Rose found the values +245.7 and 166°. Fischer found a melting point of 169 to 171°.

(2) α-METHYL *l*-ARABINOSIDE.—This substance is contained in the methyl alcoholic mother liquor from the original crystallization of the β-arabinoside. The solution was evaporated under reduced pressure to a thin sirup and kept in a vacuum desiccator, where it slowly crystallized. At successive stages of the crystallization the crystals were filtered off by suction; the $[\alpha]_D^{20}$ values of the successive crops were about the same, approximately +49, a rotation which seemed to indicate that the crystals were a mixture of the two isomers. The

separation of the pure α-isomer from this mixture was at last accomplished through the use of boiling ethyl acetate as a solvent, as it was found that the α-isomer was more soluble than the β-form. On successive fractional recrystallizations from ethyl acetate the more slowly crystallizing portions regularly showed lower specific rotations, which became constant at $[\alpha]_D^{20} = +17.3$ (0.8536 g of substance, 25 cc of aqueous solution, reading 1.18° to the right in a 1-dm tube). This is taken as the specific rotation of pure α-methyl *l*-arabinoside.

The melting point of pure α-methyl *l*-arabinoside is 131°. A preparation showing $[\alpha]_D^{20} = +20$ melted at 130°, one showing $[\alpha]_D^{20} = +49$ at 123°. Fractions giving $[\alpha]_D^{20}$ higher than +60 did not melt sharply. Purdie and Rose reported 115 to 117° as the melting point of their preparation. Proof that their product having $[\alpha]_D^{20} = +73$ was in all probability a mixture is given by the fact that on successive recrystallizations of a fraction having approximately this rotation, the $[\alpha]_D^{20}$ values of the recrystallized products gave the series $+75 \rightarrow +34 \rightarrow +20 \rightarrow +17.7 \rightarrow +17.3$.

Anal. Subs. ($[\alpha]_D^{20} = +17.3$), 0.2728: H_2O, 0.1745; CO_2, 0.4420. Calcd.: C, 44.18; H, 7.15. Found: C, 43.88; H, 7.37.

Summarizing, the following values have been found for the specific rotations of the four pure substances in dilute aqueous solution: α-methyl *d*-xyloside, $[\alpha]_D^{20} = +153.9$, α-methyl *l*-arabinoside, $[\alpha]_D^{20} = +17.3$; β-methyl *d*-xyloside, $[\alpha]_D^{20} = -65.5$, β-methyl *l*-arabinoside, $[\alpha]_D^{20} = +245.5$.

My thanks are expressed to Dr. D. H. Brauns for the skillful assistance that he has rendered in the course of the experiments.

7. THE METHYL GLYCOSIDIC DERIVATIVES OF THE SUGARS [52]

The developments that have followed from the discovery of the methyl glycosides [53] in 1893 by Emil Fischer [54] are of much historical interest. His study of the composition and reactions of these crystalline compounds which result from the union of the reducing sugars with methyl alcohol led him to conclude that they are not of the acetal type of structure, which he had expected they would prove to be, but that the semiacetal ring structure should be assigned to them. He then drew from the Van 't Hoff-LeBel theory of the asymmetric carbon atom the deduction that carbon 1 in such a ring must be asymmetric, and concluded therefore that two isomeric forms of the glycosides must be expected. He showed, likewise, that if the reducing sugars have this ring structure, a view which Tollens [55]

[52] C. S. Hudson, Jour. Am. Chem. Soc., **47**, 268–280; 1925.

[53] Following the practice of several writers the word "glycoside" is here used as a convenient class name for the various aldosides (glucosides, galactosides, maltosides, etc.) and ketosides (fructosides, sorbosides, etc.). This use was proposed by Van Rijn in 1900 in his treatise Die Glykoside.

[54] Fischer, Ber., **26**, 2400; 1893.

[55] Tollens, Ber., **16**, 921; 1883.

had suggested from rather uncertain indications some years before, two such isomeric forms of them must be assumed. These conclusions have been fully verified. The numerous α and β forms of the sugars and their derivatives that are now known represent the type of isomers that Fischer predicted. He adopted Tollens' suggestion that the union between the monosaccharides in the structures of the compound sugars is of the semiacetal ring form and this idea of the "glycosidic union" has proved to be correct. The widespread occurrence of this linkage in the synthetic and natural glycosides and compound sugars causes it to be regarded to-day as one of the most important structural features of the carbohydrates. These far-reaching consequences have come from Fischer's discovery of the methyl glycosides, by which Tollens' formula received an experimental basis and a correlation with the theory of the asymmetric carbon atom.

When the writer showed in 1909[56] that Van't Hoff's hypothesis of optical superposition applies fairly closely to the rotations of some typical substances of the sugar group the proof was based upon the comparison of the rotations of the α and β forms of glucose, galactose, lactose, methyl and ethyl glucoside and galactoside and methyl xyloside—14 substances in all.[57] From the good agreement between theory and observation it appeared probable that the principle might apply to many other substances of the sugar group and be of use in the study of structure. Accordingly, the preparation in pure form of a large number of sugar derivatives was begun and in a series of researches extending through the subsequent 15 years it has been shown that the principle of optical superposition applies so generally in the sugar group that its use furnishes a valuable method for studying structural questions. From the data that were obtained in these investigations the principal coefficients that are now used in comparing rotations in the sugar group were derived. Reference may be made to the results that have come in this field from like researches by Bourquelot[58] in comparing the rotations of many glucosides and galactosides, by Irvine[59] in studying the α and β forms of the methylated sugars and glucosamine, and by Levene[60] in classifying the aldosamines and many related substances. It seems reasonably certain from these various investigations that Van't Hoff's hypothesis applies, in first approximation at least, to the sugars and many diverse types of their derivatives.

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[56] Hudson, Jour. Am. Chem. Soc., **31**, 66; 1909.

[57] The inclusion of arabinose in the experimental data of the 1909 article was a mistake. The low-rotating α form of *l*-arabinose has never been crystallized.

[58] Bourquelot, (*a*) Ann. chim., **4**, 310; 1915; (*b*) **7**, 218; 1917.

[59] Irvine and Scott, J. Chem. Soc., **103**, 575; 1913. Irvine and Hogg, ibid., **105**, 1386; 1914. Irvine and Earl, ibid., **121**, 2370; 1922.

[60] Levene, "Hexosamines, Their Derivatives and Mucins and Mucoids," Monograph No. 18, The Rockefeller Institute for Medical Research, New York, 1922.

In applying the method of comparing rotations a number of exceptions have been found where theory and observation do not agree. The most striking of these disagreements was lately removed by the reinvestigation of the chloro- and bromo-acetyl derivatives of arabinose, as described in article 5. Experimental work in connection with another prominent disagreement, namely, the exceptional rotation of α-methyl-*l*-arabinoside, was performed in 1917. Through unavoidable circumstances it has not been possible to publish the results until the present time. They are recorded in article 6, immediately preceding this article. Meanwhile, Maltby [61] has called attention to the exceptional rotation of this arabinoside, a matter which had not previously received publication, although the writer had obviously known of it previous to 1917. In the present article the new data of article 7 will be discussed and occasion will also be taken to refer to the rotatory powers of nearly all the known methyl glycosides of the sugars.

(a) THE ROTATION OF THE TERMINAL ASYMMETRIC CARBON ATOM IN THE METHYL GLUCOSIDES, GALACTOSIDES, XYLOSIDES, AND ARABINOSIDES

It is now possible to revise the experimental test of the applicability of the principle of optical superposition to the rotations of the methyl glycosides that was originally published in 1909, by the use of the accurate measurements of Bourquelot [62] for the two forms of

TABLE 33.—*Proof of the applicability of the principle of optical superposition to the methyl glucosides, galactosides, xylosides, and arabinosides*

Substance	Molecular weight	$[\alpha]_D$ in water	$[M]_D$	Difference $2a_{Me}$	Sum
α-Methyl *d*-glucoside	194	157.9	30,630	36,930	24,330
β-Methyl *d*-glucoside	194	−32.5	−6,300		
α-Methyl *d*-galactoside	194	192.7	37,380	37,460	37,300
β-Methyl *d*-galactoside	194	−.4	−80		
α-Methyl *d*-xyloside	164	153.9	25,240	35,980	14,500
β-Methyl *d*-xyloside	164	−65.5	−10,740		
α-Methyl *l*-arabinoside	164	17.3	2,840	[1] −37,420	43,100
β-Methyl *l*-arabinoside	164	245.5	40,260		
Average				36,950, hence a_{Me} =18,500	

[1] For the explanation of the minus sign, which is a consequence of the system of nomenclature, see article 5.

methyl glucoside and galactoside and those of the preceding article for the methyl xylosides and arabinosides. It will be recalled that optical superposition requires that the difference of the molecular rotations for the four pairs of substances be a constant quantity.

The extreme values of the difference diverge by about 4 per cent only and it may be concluded that the principle applies closely. Any

[61] Maltby, J. Chem. Soc., **123**, 1404; 1923. [62] Bourquelot, Ann. Chim., **7**, 218; 1917.

test to determine the limit of applicability of the principle to these compounds will obviously require a consideration of the influences of temperature, concentration, wave length, solvent, etc., on the rotations. The exceptional rotations of the pair of methyl arabinosides to which Maltby has called attention are now replaced by new values that agree with the theory.

TABLE 34.—*The values of* $a_{Me}-a_{OH}$ *for various sugars and their methyl glycosides*

Substance	Molecular weight	$[\alpha]_D$ in water	$[M]_D$	$a_{Me}-a_{OH}$
α-Methyl *d*-glucoside	194	157.9	30,630	10,290
α-*d*-Glucose [1]	180	113	20,340	
β-Methyl *d*-glucoside	194	−32.5	−6,300	−9,700
β-*d*-Glucose [1]	180	19	3,400	
α-Methyl *d*-galactoside	194	192.7	37,380	11,460
α-*d*-Galactose [1]	180	144	25,920	
β-Methyl *d*-galactoside	194	−.4	−80	−9,440
β-*d*-Galactose [1]	180	52	9,360	
β-Methyl *d*-fructoside [2]	194	−172	−33,400	−9,500
β-*d*-Fructose [1]	180	−133	−23,900	
α-Methyl *d*-mannoside [3]	194	79	15,330	9,930
α-*d*-Mannose [4]	180	30	5,400	
α-Methyl *l*-rhamnoside [5]	178	−62.5	−11,120	−9,860
α-*l*-Rhamnose [1]	164	−7.7	−1,260	
β-Methyl *d*-α-glucoheptoside [5]	224	−74.6	−16,710	−10,750
β-*d*-α-Glucoheptose [1]	210	−28.4	−5,960	
β-Methyl gentiobioside [6]	356	−36	−12,820	−9,060
β-Gentiobiose [7]	342	−11	−3,760	
α-Methyl *d*-xyloside	164	153.9	25,240	11,440
α-*d*-Xylose [1]	150	92	13,800	
β-Methyl cellobioside [8]	356	−18.9	−6,700	−12,170
β-Cellobiose [1]	342	16	5,470	
β-Methyl *l*-arabinoside	164	243.5	40,260	14,010
β-*l*-Arabinose [1]	150	175	26,250	

[1] Hudson and Yanovsky, Jour. Am. Chem. Soc., **39,** 1035; 1917.
[2] Hudson and Brauns, ibid., **38,** 1216; 1916.
[3] Van Ekenstein, Rec. trav. chim., **15,** 223; 1896.
[4] Levene, Jour. Biol. Chem., **57,** 329; 1923.
[5] Fischer, Ber., **28,** 1145; 1895.
[6] Hudson and Johnson, Jour. Am. Chem. Soc., **39,** 1272; 1917.
[7] Bourquelot and Hérissey, J. pharm. chim. [6], **16,** 418; 1902. See Jour. Am. Chem. Soc., **38,** 1569; 1916.
[8] Helferich, Loewa, Nippe and Riedel, Z. physiol. Chem., **128,** 149; 1923.

(b) COMPARISON OF THE ROTATIONS OF VARIOUS METHYL GLYCOSIDES WITH THOSE OF THE RESPECTIVE SUGARS

Quite a number of methyl glycosides have been isolated in only one modification. Some idea of the applicability of the principle to their rotations can in many cases be obtained from a comparison of the molecular rotation of a given glycoside with that of its parent sugar. Since the rotation of an α-methyl glycoside of a sugar of the *d*-series is written $b+a_{Me}$ and that of the α form of the parent sugar $b+a_{OH}$ the difference is $a_{Me}-a_{OH}$, and the similar difference for the respective β compounds is $-(a_{Me}-a_{OH})$. The signs of the differences are the reverse of these if the sugar is of the *l*-series. It is to be expected that these differences will have the same numerical value and the proper signs, throughout the sugar group. The question of

the correctness of this conclusion from the theory may be judged by a consideration of the data of Table 34.

In all cases the sign of the difference is correct. Eight of the 12 pairs show a fairly constant value for the difference. The explanation of the larger values for the remaining four pairs must be left to future investigation. The fact that a better purification of the respective forms of the four sugars must be expected to cause these larger differences to approach the normal average is suggestive, since there can be little doubt that some of the sugars have not yet been obtained in pure α and β forms.

It is a very noteworthy fact that the normal value of the difference holds for mannose and rhamnose. These sugars and lyxose are closely related in configuration, and it has been shown that the three exhibit a considerable and similar deviation from the principle of optical superposition when the rotations of their respective α and β forms are compared.[63] On the basis of the present experimental results it is suggested that the known α forms of mannose ($[\alpha]_D = +30$) and methyl mannoside ($+79$), rhamnose (-7.7) and methyl rhamnoside (-62.5), and lyxose ($+5.5$) and benzyl lyxoside ($+80.5$) (see the next section of this article) possess ring structures common to the respective members of each pair (and possibly common also to the three pairs). Such an hypothesis accounts for the observed agreements of the rotations with the principle in these cases. At the same time it is suggested that the β forms of these sugars, the rotations of which have been shown to differ from those of the respective α forms by a much smaller amount than is required by the principle, possess rings that are different from those of the α forms. This view will be more fully developed in a subsequent article through the further comparison of many rotatory measurements that strongly support it.

(c) METHYL *d*-LYXOSIDE

This crystalline substance was prepared by Van Ekenstein and Blanksma [64] by the interaction of lyxose and acidified methyl alcohol. Its specific rotation is recorded as $+40.2$. Since this value is more dextrorotatory than that of α-*d*-lyxose ($+5.5$ changing to -14 final)[65] the glycoside is to be classed as an α form. The specific rotation of methyl *d*-lyxoside can be calculated in three independent ways, (1) from the rotation of α-*d*-lyxose, (2) from that of α-methyl *d*-xyloside, and (3) from that of benzyl lyxoside.

(1) Calculation by the First Method.—The molecular rotation of α-*d*-lyxose (mol. wt., 150) is $b_{lyxose} + a_{OH} = 5.5(150) = 825$ and hence $b_{lyxose} = -7{,}675$, since a_{OH} has the value 8,500 (see article 3,

[63] Hudson and Yanovsky, Jour. Am. Chem. Soc., **39**, 1035; 1917.
[64] Van Ekenstein and Blanksma, Z. Ver. deut. Zucker-Ind., **58**, 114; 1908.
[65] Hudson and Yanovsky, Jour. Am. Chem. Soc., **39**, 1035; 1917.

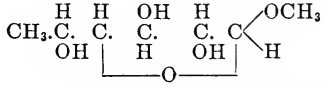
p. 334). The specific rotation of α-methyl *d*-lyxoside (mol. wt., 164) then becomes $(b_{lyxose} + a_{Me}) \div$ mol. wt. $= (-7{,}675 + 18{,}500) \div 164 = +66$.

(2) CALCULATION BY THE SECOND METHOD.—Since the α forms of methyl *d*-lyxoside and methyl *d*-xyloside are epimers, they differ in structure like the α forms of methyl *d*-mannoside and methyl *d*-glucoside and the differences between the molecular rotations of the members of each epimeric pair should be the same. Hence the specific rotation of α-methyl *d*-lyxoside is $(25{,}240 + 15{,}330 - 30{,}630) \div 164 = +61$.

(3) CALCULATION BY THE THIRD METHOD.—Van Ekenstein and Blanksma prepared crystalline benzyl *d*-lyxoside (mol. wt., 240) from the sugar and acidified benzyl alcohol and found its specific rotation to be + 80.5 in water. The high dextrorotation indicates that the glycoside is an α form and its molecular rotation is accordingly $b_{lyxose} + a_{Bz} = 80.5\ (240) = 19{,}300$. The molecular rotation of β-benzyl *d*-glucoside ($[\alpha]_D = -55.7$ in water,[66] mol. wt., 270) is $b_{glucose} - a_{Bz} = -55.7\ (270) = -15{,}040$, and since $b_{glucose} = 11{,}880$, $a_{Bz} = 26{,}900$, and $b_{lyxose} = -7{,}620$, a value which agrees closely with that found previously from the rotation of α-methyl *d*-lyxose. Using the value from the benzyl lyxoside, which has just been shown to agree with the principle of optical superposition, the specific rotation of α-methyl *d*-lyxoside is calculated to be $(-7{,}620 + 18{,}500) \div 164 = +66$. The agreement of the three calculated values makes it appear very likely that Van Ekenstein and Blanksma's methyl lyxoside was not a pure α form but contained some other substance, probably the β isomer. The matter is of considerable importance because it relates to the difference of the rotations of epimers in the sugar group.

(d) BETA-METHYL *d*-ISORHAMNOSIDE

This crystalline substance was prepared by Fischer and Zach [67] by the saponification of its triacetate, which was made by the reduction of 6-bromo-2,3,5-triacetyl β-methyl glucoside, which in turn was made from di-bromo-acetyl glucose (Structure XVI of article 1; see also article 5) by Koenigs and Knorr's synthesis. Fischer and Zach have designated it a β-glycoside because they found that emulsin hydrolyzes it; it will be seen from the following considerations of rotatory data that this designation is correct. The configuration of β-methyl *d*-isorhamnoside is



(1)

[66] Fischer and Helferich, Ann., 383, 68; 1911.

[67] Fischer and Zach, Ber., 45, 3767; 1912.

If the rotation of the β form of isorhamnose were known the value of $(A'_{Me}—A'_{OH})$ could be found, but the β form has not been crystallized. There is another way, however, through which the applicability of the principle of optical superposition to this glycoside of isorhamnose can be tested, and the result shows that the principle applies. It is seen from the structural formula (I) of the glycoside that *d*-isorhamnose itself is a reduced *d*-glucose. Likewise it is known that *d*-rhamnose (that is, the antipode of natural *l*-rhamnose) is to be considered a reduced *d*-mannose.[68] If the change in structure from a methyl mannoside to the corresponding methyl rhamnoside causes a change in rotation of Y it is to be expected that the same change will be found in the case of the rotations of methyl glucoside and methyl isorhamnoside, if like changes in structure cause like changes in rotation, a rule which may be deduced from the principle of optical superposition, as was shown in article 4. The comparisons are recorded in Table 35 for the respective pairs of methyl glycosides. The rotation of methyl *d*-rhamnoside is written as equal to that observed for methyl *l*-rhamnoside but of reverse sign.

TABLE 35.—*The related rotations of corresponding methyl glycosides of d-glucose, d-isorhamnose, d-mannose, and d-rhamnose*

Substance	Molecular weight	$[\alpha]_D$ in water	$[M]_D$	Difference
β-Methyl *d*-glucoside	194	−32.5	−6,300	+3,500
β-Methyl *d*-isorhamnoside	178	−55.2	−9,800	
α-Methyl *d*-mannoside	194	79	15,300	+4,200
α-Methyl *d*-rhamnoside	178	62.5	11,100	

The differences for the two pairs of glycosides are nearly alike, the variation of 700 corresponding to only about four degrees in specific rotation. The agreement with theory proves that the known methyl *d*-isorhamnoside is a β form, confirming Fischer and Zach's classification.[69] In article 5 it was shown that 6-bromo-1,2,3,5-acetyl glucose is a β-acetate and its production by the interaction of dibromo-acetyl glucose and silver acetate follows the rule that Koenigs and Knorr's reaction yields β derivatives. It is now shown that the similar glycoside synthesis from dibromo-acetyl glucose yields the β derivative. Since these two syntheses thus follow the usual course of Koenigs and Knorr's reaction it seems very probable that the Walden inversion that was shown in article 1 to accompany this reaction likewise occurs here, that dibromo-acetyl glucose is an α form and

[68] Fischer and Zach, loc. cit. Hudson, Jour. Am. Chem. Soc., **31**, 338; 1910.

[69] It would be interesting to compare the rotations of the acetates of these four methyl glycosides, all of which have been prepared in pure form, but unfortunately they have not been measured in the same solvent, chloroform having been used for two of them, alcohol for the third and acetylene tetrachloride for the fourth. This example again emphasizes the importance of measuring the rotations of new substances in chloroform or water whenever possible (see articles 1 and 5).

that its rotation, which has not yet been measured, will be found to be near the value that has been calculated in articles 1 and 5 on this supposition, +193 in chloroform. (See footnote 37, p. 347.)

(e) CALCULATION OF THE ROTATIONS OF THE FORMS OF *d*-ISORHAMNOSE

From the molecular rotation of β-methyl *d*-isorhamnoside, $[M]_D = b_{isorhamnose} - a_{Me} = -9{,}800$, and the value of a_{Me} from Table 33 the rotation of the basal chain of the methyl pentose is $b_{isorhamnose} = 8{,}700$ in water. The molecular and specific rotations of the α and β forms of the sugar (mol. wt., 164) are calculated from this value and the rotation (a_{OH}) of the end asymmetric carbon atom (8,500, see article 3, p. 334) to be α-*d*-isorhamnose, $[M]_D = 8{,}700 + 8{,}500 = 17{,}200, [\alpha]_D = +105$; β-*d*-isorhamnose, $[M]_D = 8{,}700 - 8{,}500 = 200$, $[\alpha]_D = +1$.

Fischer and Zach crystallized *d*-isorhamnose and recorded one measurement of the course of its mutarotation, $[\alpha]_D$ five minutes after solution in water being 73 and the final value being 29.7. The readings that were made at intermediate times do not show a constant coefficient for a unimolecular reaction, from which it seems probable that the temperature varied during the mutarotation. By extrapolation the writer obtains an initial value of about 83, which is at best only a minimum value and will doubtless be increased considerably when more careful observations and a better purification of the sugar are obtained. Such has indeed been the usual result when even such well-known sugars as glucose and lactose were carefully studied with the object of obtaining pure α and β forms. It is probable, therefore, that the calculated value for crystalline α-*d*-isorhamnose is more reliable than that measured by Fischer and Zach. Their value of the final rotation lies between those calculated for the two forms, as would be expected.

(f) METHYL FUCOSIDE

Tadokoro and Nakamura [70] have recently described the preparation of a crystalline methyl *l*-fucoside by the action of acidified methyl alcohol on *l*-fucose and record its $[\alpha]_D = -122$ in water. The final rotation of *l*-fucose is -75; hence the fucoside is to be named an α form because its rotation is more levorotatory than that of the parent sugar of the levo series. It has been shown by Clark [71] that the configuration of *l*-fucose is that of a reduced *l*-galactose, the group CH_2OH of the hexose becoming CH_3 in the methyl pentose. There are two independent ways by which the rotation of this fucoside can be calculated—first, from the rotation of α-methyl *d*-galactoside; and second, from the rotation of α-*l*-fucose.

[70] Tadokoro and Nakamura, J. Biochem. (Japan), **2**, 461; 1923.
[71] Clark, Jour. Biol. Chem., **54**, 65; 1922.

(1) Calculation by the First Method.—The configuration of carbon 5 is the same for *d*-glucose, *d*-mannose, and *d*-galactose if the butylene ring structure (or the amylene) is assumed for the three sugars. The reduction of the primary alcohol group attached to the symmetric carbon 6 of *d*-glucose and *d*-mannose causes an increased molecular levorotation of about 4,000 (see Table 35), and it may be assumed on good grounds that this change is mainly referable to the adjacent carbon 5. Therefore α-methyl *d*-fucoside may be expected to rotate more levo by 4,000 than α-methyl *d*-galactoside, that is, $[M]_D = 37,380 - 4,000 = 33,380$, and the molecular rotation of its antipode, α-methyl *l*-fucoside, is then $-33,380$ and its $[\alpha]_D = -33,380 \div 178 = -188$.

(2) Calculation by the Second Method.—Tollens and Rorive [72] have recorded the rotation of α-*l*-fucose in water 10 minutes after dissolving as -124.1, which changed gradually to become constant at -75.6. From the mutarotation curve they obtained by graphical extrapolation the value -150 for the initial rotation, but this method is not reliable in the case of an extensive extrapolation. By using the equation for a unimolecular reaction the extrapolated value is -144, which seems more reliable. The molecular rotation of α-*l*-fucose is $(b_{l\text{-fucose}} - a_{OH}) = -(144)(164) = -23,600$ and hence $b_{l\text{-fucose}} = -15,100$. For α-methyl *l*-fucoside $[\alpha]_D = (b_{l\text{-fucose}} - a_{Me}) \div$ mol. wt. $= (-15,100 - 18,500) \div 178 = -190$, which agrees well with the previously calculated value. It seems probable that Tadokoro and Nakamura's methyl fucoside preparation was a mixture of the α and β isomers.

(g) Methyl Maltoside and its Hepta-acetate

Hudson and Sayre [73] have calculated the specific rotation of β-methyl maltoside hepta-acetate to be $(B_{maltose} - A_{Me}) \div$ mol. wt. $= (62,700 - 26,900) \div 650 = +55$, which agrees almost exactly with the value which they observed for the pure substance in chloroform, $+54$. By the saponification of this acetate Fischer and Armstrong [74] obtained β-methyl maltoside in amorphous form but were unable to crystallize it. The calculated specific rotation of the substance is derived as follows: The molecular rotation of β-maltose is $(b_{maltose} - a_{OH}) = (118)(342) = 40,400$, hence $b_{maltose} = 48,900$, and the specific rotation of β-methyl maltoside is $(b_{maltose} - a_{Me}) \div$ mol. wt. $= (48,900 - 18,500) \div 356 = +85$ in water. The value observed by Fischer and Armstrong was $+70$, but the material was amorphous and it seems probable that if the pure crystalline substance could be obtained it would give a higher value. Indeed, they do not accept their observed value as being the correct rotation of the pure isomer.

[72] Tollens and Rorive, Z. Ver. deut. Zucker-Ind., **59**, 579; 1909

[73] Hudson and Sayre, Jour. Am. Chem. Soc., **38**, 1867; 1916.

[74] Fischer and Armstrong, Ber., **34**, 2885; 1901. (Irvine and Black (J. Chem. Soc., **129**, 874; 1926) have lately found $[\alpha]^D = +83.9$ in water for pure recrystallized β-methyl maltoside, in good agreement with the predicted value.)

(h) ETHYL MALTOSIDE, ETHYL GLUCOSIDE, AND THE VALUE OF A_{Et}

Although the present article does not deal with the ethyl glycosides, reference may here be made to β-ethyl maltoside because from its rotation, which has been accurately measured recently by H. Fischer and Koegl,[75] that of β-methyl maltoside can be calculated by an independent way. By the saponification of hepta-acetyl ethyl maltoside, which was prepared from amorphous bromo-acetyl maltose ($[\alpha]_D = +71$ in chloroform) by Koenigs and Knorr's method, they obtained crystalline ethyl maltoside ($[\alpha]_D = +79.22$ in water, mol. wt., 370; hence $[M]_D = 29{,}310$). It is probable from the method of synthesis that it is a β-glycoside and this allocation is confirmed by the following calculation. To derive its rotation it is necessary to know the value of a_{Et}, the rotation of the end asymmetric carbon atom of the ethyl glycosides. This can be found from the accurately known rotation of α-ethyl glucoside (mol. wt., 208) which Fischer [76] found to be 150.6 and Bourquelot [77] on revision 150.9. Its molecular rotation is $(b_{glucose} + a_{Et}) = (150.9)\ 208 = 31{,}390$, and since $b_{glucose} = 11{,}880$, *$a_{Et} = 19{,}510$ in water.* The specific rotation of β-ethyl maltoside is then calculated to be $(b_{maltose} - a_{Et}) \div 370 = (48{,}900 - 19{,}510) \div 370 = +79.4$, in good agreement with the observed value. The specific rotation of β-methyl maltoside is likewise calculated from these data to be $(b_{maltose} - a_{Et}) + (a_{Et} - a_{Me}) \div 356 = (29{,}310 + 19{,}510 - 18{,}500) \div 356 = +85$, which agrees completely with the value calculated in the preceding section.

(i) METHYL LACTOSIDE AND ITS HEPTA-ACETATE

The specific rotation of the β form of hepta-acetyl methyl lactoside (mol. wt., 650) is $B_{lactose} - A_{Me} = (16{,}900 - 26{,}900) \div 650 = -15$ in chloroform, from the data of article 1. Ditmar [78] prepared this substance by Koenigs and Knorr's synthesis, and the crystalline material which resulted from the action of methyl alcohol on chloro-acetyl lactose showed $[\alpha]_D = +6$, while from bromo-acetyl lactose a derivative of $[\alpha]_D = -6$ was obtained. Judging from rotatory data, both preparations were probably impure β-hepta-acetyl methyl lactoside.

By the saponification of the acetate Ditmar prepared the methyl lactoside and described it as a crystalline substance, m. p. 170 to 171°, but no record of its rotation is mentioned. The substance is doubtless the β form, the specific rotation of which is calculated as follows: The molecular rotation of β-lactose is $b_{lactose} - a_{OH} = 35(342) = 11{,}970$; hence $b_{lactose} = 11{,}970 + 8{,}500 = 20{,}470$, and the specific rotation of β-methyl lactoside becomes $(b_{lactose} - a_{Me}) \div$ mol. wt. $= (20{,}470 - 18{,}500) \div 356 = +6$ in water.

[75] H. Fischer and Koegl, Ann., **436**, 219; 1924.
[76] Fischer, Ber., **28**, 1145; 1895.
[77] Bourquelot, Ann. chim., **7**, 218; 1917.
[78] Ditmar, Ber., **35**, 1951; 1902.

(j) METHYL *l*-SORBOSIDE

This substance (mol. wt., 194) was prepared by Fischer [79] who records $[\alpha]_D = -88.7$ in water, and the molecular rotation is accordingly $-17{,}200$. It has been shown [80] that this high negative rotation indicates that the substance is an α form because sorbose, a sugar of the levo series, rotates only -43. Sorbose does not show mutarotation. The specific rotation of α-*l*-sorbose is calculated from that of the sorboside in the usual manner to be $[(b_{sorbose} - a_{Me}) + (a_{Me} - a_{OH})] \div$ mol. wt. $= (-17{,}200 + 18{,}500 - 8{,}500) \div 180 = -40$, a value quite near the observed rotation of sorbose. This result apparently indicates that the rotation -43 is the true rotation of α-*l*-sorbose and is not an equilibrium rotation such as is the value 52 for glucose or -92 for fructose, because the final rotations of the many mutarotating sugars are in all cases widely different from the rotations of their α and β forms. Such a conclusion deserves a careful consideration but it should be regarded as an indication only, not a proof, until it can be tested in some independent way, because it would be very surprising if sorbose does not establish an equilibrium between its α and β forms in the way that the related ketoses, fructose and perseulose are known to do. It is remarked, however, that fructose and perseulose are the only crystalline ketoses which have been observed to mutarotate. On the other hand, fructose tetra-acetate, which would be expected to exhibit mutarotation because glucose tetra-acetate does, shows a constant rotatory power.[81] Mutarotation has not been detected so far for tagatose, mannoketoheptose or sorbose. Sedoheptose crystallizes as a nonreducing anhydro-sedoheptose which would not be expected on structural grounds to show mutarotation. The writer has supposed in the past that the mutarotation of tagatose, mannoketoheptose and sorbose was so rapid that it had escaped detection, and this view receives support from the fact that fructose mutarotates very rapidly indeed. The rotatory relations that have just been disclosed suggest, however, a different explanation, namely, that sorbose does not isomerize in solution like fructose and the aldoses.[82] Obviously the subject requires further experimental study. It seems practically certain that the recorded rotations of both sorbose and methyl sorboside are substantially correct because the rotation of the sugar has been measured by several observers with agreeing results, and the antipodal forms (*d*-sorbose and methyl *d*-sorboside)

[79] Fischer, Ber., **28**, 1145; 1895.

[80] Hudson and Brauns, Jour. Am. Chem. Soc., **38**, 1216; 1916.

[81] Hudson and Brauns, Jour. Am. Chem. Soc., **37**, 2742; 1915.

[82] Levene, J. biol. Chem., **59**, 135; 1924; has recently made the novel suggestion that the apparent absence of mutarotation in the case of 2,5-anhydro-glucose and the certain absence of lactone formation in the cases of, 2,5-anhydro-gluconic and 2,5-anhydro-mannonic acids is due to a spatial interference of the 2,5 ring structure with the formation of the 1,4 ring that is assumed for the α and β forms of glucose and for the lactones of gluconic and mannonic acids.

have been found to rotate +43 and +88.5.[83] There is another hypothesis, however, which offers an explanation of the present anomaly without excluding the possibility that sorbose may show very rapid mutarotation. The methyl sorboside may possess a ring structure different from that of sorbose. It would not be surprising if this explanation should prove correct, because the researches of the day are rapidly disclosing many examples of new ring structures among the substances of the sugar group. It seems premature to say more than that the comparison of rotations has disclosed in the case of sorbose and the other ketoses an interesting problem.

Nearly all the known methyl glycosides of the sugars proper have now been considered. For the sake of completeness it is mentioned that the omitted ones are methyl riboside, which is known only as an impure sirup, the methyl glycosides of the so-called γ forms of some of the sugars, the recently discovered isomers of methyl rhamnoside and methyl mannoside, the two forms of methyl glucodesoside, and the methyl glycosides of 6-bromo, 6-amino, and 3,6-anhydro glucose, and of glucosamine and epiglucosamine. The rotations of some of these will be discussed at a later time; the consideration of them requires in some cases the obtaining of new experimental data and in others the presentation first of a further development of the method (article 4) of classifying structurally similar derivatives of different sugars.

(k) SUMMARY

From Bourquelot's measurements of the rotations of the methyl glucosides and galactosides and those of the methyl xylosides and arabinosides recorded in the preceding article (article 6) it is found that Van 't Hoff's principle of optical superposition holds closely for these substances, the maximum deviation being about 4 per cent (Table 33). The results confirm the writer's conclusion, in 1909, that the principle applies, as a first approximation at least, to the rotations of the methyl glycosides. The rotations of the methyl arabinosides, which in the past have been considered exceptional, are now shown to conform to the principle.

By comparing the rotation of a methyl glycoside with that of its parent sugar (Table 34) it is shown that the principle likewise applies closely to β-methyl fructoside, α-methyl mannoside, α-methyl rhamnoside and β-methyl gentiobioside. The known form of methyl α-glucoheptoside is classified in the β-series from rotatory data.

The specific rotation of α-methyl *d*-lyxoside is calculated by three independent ways to be +66, +61 and +66; these values agree well

[83] Lobry de Bruyn and Van Ekenstein, Rec. trav. chim., **16**, 262; 1897; **19**, 1; 1900; Van Ekenstein and Blanksma, ibid., **27**, 1; 1908.

with one another but deviate greatly from the value of +40 measured by Van Ekenstein and Blanksma. Benzyl *d*-lyxoside ($[\alpha]_D = +80.5$) is classified as an α form; its rotation agrees with the theory.

Fischer and Zach's classification of methyl *d*-isorhamnoside as a β form from the fact that emulsin hydrolyzes it, is confirmed through rotatory data (Table 35), which likewise prove that the principle applies to its rotation. The rotations of the α and β forms of *d*-isorhamnose are calculated and the results compared with Fischer and Zach's measurements.

It is shown that Tollens and Rorive's curve for the mutarotation of fucose indicates −144 rather than their extrapolated value −150 as the intial specific rotation of α-*l*-fucose. The rotation of α-methyl *l*-fucoside is calculated in two independent ways to be −188 and −190. These agreeing values indicate that the rotation recently found by Tadokoro and Nakamura, −122, may refer to a mixture of the α and β isomers.

The rotation of β-methyl maltoside is calculated by two independent ways to be +85. The value +70 has been recorded by Fischer and Armstrong for an amorphous and probably impure preparation of the substance. (See footnote 74, p. 363). The calculated rotation of β-ethyl maltoside (+79.4) agrees closely with that recently observed by H. Fischer and Koegl (+79.2) who prepared the substance in pure crystalline form. In this calculation the new coefficient a_{Et}, the rotation of the end asymmetric carbon atom of the ethyl glycosides, has been found to have the value +19,440 in water, from Fischer's measurement of the rotation of α-ethyl glucoside, which was confirmed by Bourquelot.

The rotations of β-methyl lactoside and its hepta-acetate, substances which were crystallized by Ditmar but not accurately purified, are calculated to be +6 and −15, respectively.

The relation of the rotation of methyl sorboside to that of sorbose is shown to indicate either (1) that sorbose, a ketose for which mutarotation has not been detected so far, persists in solution as its α form, or (2) that sorbose and methyl sorboside possess different ring structures.

8. SOME TERPENE ALCOHOL GLYCOSIDES OF GLUCOSE, GLUCURONIC ACID, MALTOSE, AND LACTOSE [84]

Most of the numerous glycosides that have been isolated from plants, such as amygdalin, salicin, arbutin, coniferin, quercitrin, etc., are combinations of reducing sugars (glycoses) with alcoholic or phenolic substances of the aromatic series, although a few aliphatic glycosides have been found, such as linamarin of the flax plant (acetone-cyanohydrin glucoside) and sinigrin of black mustard seed.

[84] C. S. Hudson, Jour. Am. Chem. Soc., **47**,537-543; 1925.

While many glycosides of the commoner aliphatic alcohols have been synthesized, for example, the methyl, ethyl, propyl and glycol glucosides and galactosides, etc., such compounds have not yet been found in nature.[85] Since the phenyl glycoside of glucuronic acid has been found to be a normal constituent of the urine of various animals, it seems probable that phenyl glucoside is a normal intermediate metabolic product which by oxidation yields phenyl-glucuronic acid (E. Fischer and Piloty).[86] Since the compound sugars are true glycosides, maltose being 1,6-α-glucosido glucose and lactose being 1,5-β-galactosido glucose, it is evident that both plants and animals synthesize glycosides of hydroxy aldehydes. Glycosidic compounds of the sugars obviously play important rôles in biological processes and it must be expected that many new glycosides will in time be isolated from natural products as well as synthesized in the laboratory.

The writer has shown in several articles[87] that Van 't Hoff's principle of optical superposition applies to the rotations of the synthetic glycosides of the aliphatic alcohols and to the rotations of the compound sugars. Although it was indicated in the first of those articles (1909) that the principle probably applied to salicin, arbutin and coniferin, precise evidence relating to aromatic glycosides was lacking until it was shown by the recent comparison of the rotations of the glycosides of the amygdalin group in article 3[88] that the principle applies closely to the glycosides of mandelonitrile. In article 7 it has been shown that it applies likewise to two other aromatic glycosides, namely, benzyl glucoside and lyxoside. It seems desirable to extend the study to glycosides of diverse types because, if it should be found that the principle applies generally to them, the method of comparing rotations can be used in classifying the structures of the members of this large group of natural products.

The present article deals with the rotations of a group of glycosides of the related terpene alcohols, menthol and borneol. The *d*-glucosides of these alcohols have been synthesized in the past, and although they have not as yet been isolated from plants or animals it seems quite probable that they may occur naturally. When menthol or borneol is fed to animals it is eliminated in the urine in the form of the corresponding glycoside of glucuronic acid; thus *l*-menthol yields *l*-menthyl-glucuronic acid. Bergmann and Wolff[89] have recently supplied conclusive proof that this substance is a β-glycoside. Starting with the α form of *l*-menthyl glucoside (Structure I), they oxi-

[85] Wattiez (Journ. pharm. Belgique **7**, 81; 1925, through Journ. pharm. chim., **2**, 20; 1925) has recently isolated β-methyl glucoside from the leaves of *Scabiosa succisa L*

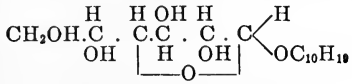
[86] E. Fischer and Piloty, Ber., **24**, 521, 1891.

[87] Hudson, Jour. Am. Chem. Soc., **31**, 66, 1909; 38, 1566; 1916; **47**, 268; 1925. Bourquelot, Ann. chim., **7**, 219; 1917; Maltby, Jour. Chem. Soc., **123**, 1404; 1923.

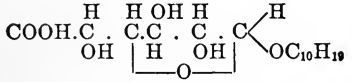
[88] Hudson, Jour. Am. Chem. Soc., **46**, 483; 1924.

[89] Bergmann and Wolff, Ber., **56B**, 1060; 1923.

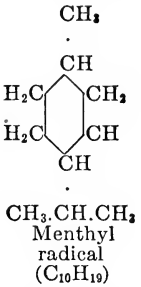
dized it *in vitro* by means of bromine in alkaline solution and obtained an α-*l*-menthyl-glucuronic acid (Structure II) that is isomeric rather than identical with the older *l*-menthyl-glucuronic acid, which must accordingly be classed as the β form. They mention that the strong dextrorotation of their α compound in contrast with the levorotation of the older form agrees with this classification. It is possible to develop this idea in a quantitative way, and it will now be shown that Bergmann and Wolff's data prove that the principle of optical



α-Menthyl *d*-glucoside (I)



α-Menthyl *d*-glucuronic acid (II)



superposition applies, in first approximation at least, to the menthyl glucosides and the menthyl-glucuronic acids and indicate that it probably applies likewise to the bornyl glucosides described by E. Fischer and Raske and Hämäläinen.

(a) THE MENTHYL AND BORNYL GLUCOSIDES AND THE MENTHYL-GLUCURONIC ACIDS

Consider the molecular rotation of α-*l*-menthyl *d*-glucoside, of Structure I. Let the rotation of the basal glucose chain be $b_{glucose}$, that of the terminal asymmetric carbon atom $a_{menthyl}$, and that of the menthyl radical, which is optically active due to the presence of three asymmetric carbon atoms, be $-c_{menthyl}$. Assuming that the principle of optical superposition holds, the rotation of the β-*l*-menthyl *d*-glucoside may be referred to the same component rotations with the sign of $a_{menthyl}$ reversed. For the α and β forms of *l*-menthyl-*d*-glucuronic acid (see the Structure II of the α form) let the three components of the rotations be $b_{glucuronic}$, $a_{menthyl}$ and $-c_{menthyl}$, similarly. In Table 36 the comparison of the rotations of the four substances in alcoholic solution is recorded, using the data of the literature.

TABLE 36.—*Comparison of the molecular rotations of the menthyl and bornyl glucosides and menthyl-glucuronic acids in alcohol*

Substance	$[\alpha]_D$	Molecular rotation	Diff./2	Sum/2
α-l-Menthyl glucoside [1]	64.2	$20,400 = b_{glu} + a_{mth} - c_{mth}$	25,100 (a_{mth})	$-4,700$ ($b_{glu} - c_{mth}$)
β-l-Menthyl glucoside [1] (mol. wt., 318).	−93.7	$-29,800 = b_{glu} - a_{mth} - c_{mth}$		
α-l-Menthyl-glucuronic acid [2]	51.8	$17,200 = b_{glr} + a_{mth} - c_{mth}$	25,950 (a_{mth})	$-8,750$ ($b_{glr} - c_{mth}$)
β-l-Menthyl-glucuronic acid [3] (mol. wt., 332).	−104.6	$-34,700 = b_{glr} - a_{mth} - c_{mth}$		
β-d-Bornyl glucoside [4]	−44.6	$-14,100 = b_{glu} - a_{brn} + c_{brn}$	2,450 (c_{brn})	$-16,550$ ($b_{glu} - a_{brn}$)
β-l-Bornyl glucoside [5] (mol. wt., 316).	−60.1	$-19,000 = b_{glu} - a_{brn} - c_{brn}$		

NOTE.—The subscripts glucose, glucuronic, menthyl, and bornyl are abbreviated.

[1] E. Fischer and Bergmann, Ber., **50**, 711; 1917. See also Ref. 4.
[2] Bergmann and Wolff, Ber., **56B**, 1060; 1923.
[3] H. Fischer, Z. physiol. Chem., **70**, 262; 1911.
[4] E. Fischer and Raske, Ber., **42**, 1465; 1909. Their value of the rotation of the monohydrate has been here increased to refer to the anhydride.
[5] Hämäläinen, Biochem. Z., **50**, 209; 1913.

It will be seen that the values of $a_{menthyl}$ obtained independently, in one case from the glucosides and in the other from the glucuronic acids, agree closely (25,100 and 25,950), the difference of 850 corresponding to less than three degrees in specific rotation. The data refer to alcoholic solutions but the measurements were all made in the same solvent and it has been shown [90] that optical superposition holds for alcoholic solutions in the case of the acetyl derivatives of the methyl glucosides. The average value $a_{menthyl} = 25,500$ may therefore be accepted for alcoholic solution.

From the last column of Table 36 $b_{glucose} - c_{menthyl} = -4,700$ in alcohol. The value of $b_{glucose}$ in water is 11,880 (see article 7) and the value in alcohol is doubtless nearly the same, since such is the case for 80 per cent alcohol and for absolute methyl alcohol.[91] Subtracting this value leaves $c_{menthyl} = 16,600$ as a provisional value in alcoholic solution. It is possible from the knowledge of the values of these two coefficients to calculate approximately the rotations of the α and β forms of a large number of menthyl glycosides of the reducing sugars for which the respective values of b in water are known, about 60 menthyl glycosides in all. The calculations are illustrated by examples in the next section of this article.

From bromo-acetyl glucose and *d*-borneol Fischer and Raske prepared *d*-bornyl glucoside and similarly from *l*-borneol Hämäläinen made *l*-bornyl glucoside. From the method of synthesis (Koenigs and Knorr's) and the fact that emulsin hydrolyzes both glucosides it is almost certain that they are β compounds. From the formulation of their molecular rotations in Table 36 the value $b_{glucose} - a_{bornyl} = -16,550$ in alcohol is found and hence $a_{bornyl} = 28,400$ as a provisional value. This coefficient has about the same value as that found previously for $a_{menthyl}$ (25,100), a result which is to be expected

[90] Hudson and Dale, Jour. Am. Chem. Soc., **37**, 1264; 1915.
[91] Hudson and Yanovsky, ibid., **39**, 1013; 1917.

because menthol and borneol have similar structures and nearly the same molecular weights. The agreement proves that the bornyl glucosides are β compounds, as assumed.

It is obvious that these calculations can be extended to compounds such as fenchyl glucoside and fenchyl-glucuronic acid, the similar derivatives of phloroglucinol and many others.[92] At the present time, however, the rotations of such compounds are not known in a common solvent, and, accordingly, the calculations must be deferred until the necessary experimental data are obtained.

(b) MENTHYL MALTOSIDE AND MENTHYL LACTOSIDE

These glycosides have been prepared by E. Fischer and H. Fischer through Koenigs and Knorr's synthesis, which makes it probable that they are β forms. This conclusion is supported by the fact that menthyl lactoside is hydrolyzed by emulsin to yield menthol and lactose, according to H. Fischer. In Table 37 the calculated rotations of these glycosides are recorded in comparison with the observed values. The agreement shows that both glycosides are β forms, since the calculated values have been obtained on that assumption. For comparison the calculated rotations of the corresponding α forms are shown; the results leave no doubt concerning the classifications. It should be mentioned that the observed rotations refer to aqueous solutions, whereas the calculated values are based upon the coefficients applying to alcoholic solutions, but it is improbable that this difference affects the conclusions.

The rotations of the two forms of *l*-menthyl gentiobioside and of *d*-menthyl gentiobioside, which have not yet been prepared, are calculated for the purpose of illustrating the method. The values of $b_{maltose}$ and $b_{lactose}$ are taken from article 7, that of $b_{gentiobiose}$ from article 3.

TABLE 37.—*Calculated provisional rotations of the menthyl maltosides, lactosides, and gentiobiosides*

Substance	Calculated molecular rotation	$[\alpha]_D$	
		Calculated	Observed
α-*l*-Menthyl maltoside	$b_{maltose}+a_{mth}-c_{mth}=48,900+25,100-16,600$	+120	
β-*l*-Menthyl maltoside (mol. wt., 480).	$b_{maltose}-a_{mth}-c_{mth}=48,900-25,100-16,600$	+15	[a] +14
α-*l*-Menthyl lactoside	$b_{lactose}+a_{mth}-c_{mth}=20,470+25,100-16,600$	+60	
β-*l*-Menthyl lactoside	$b_{lactose}-a_{mth}-c_{mth}=20,470-25,100-16,600$	−44	[b] −38
α-*l*-Menthyl gentiobioside	$b_{gnbiose}+a_{mth}-c_{mth}=4,100+25,100-16,600$	+26	
β-*l*-Menthyl gentiobioside	$b_{gnbiose}-a_{mth}-c_{mth}=4,100-25,100-16,600$	−78	
α-*d*-Menthyl gentiobioside	$b_{gnbiose}+a_{mth}+c_{mth}=4,100+25,100+16,600$	+95	
β-*d*-Menthyl gentiobioside	$b_{gnbiose}-a_{mth}+c_{mth}=4,100-25,100+16,600$	−9	

[a] E. Fischer and H. Fischer, Ber., **43**, 2521; 1910.
[b] H. Fischer, Z. physiol. Chem., **70**, 262; 1911.

[92] For numerous references to the known derivatives of glucuronic acid see Abderhalden's Biochemisches Handlexikon, **2**, **8**, and **10**, under the title "Glucuronic acid."

(c) 6*x*,-ANHYDRO-*l*-MENTHYL GLUCOSIDE

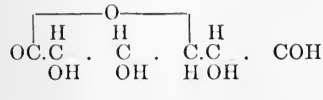
By the interaction of 1,6-dibromo-2,3,5-triacetyl glucose (dibromo-acetyl glucose, of Structure XVI, article 1[93]) and *l*-menthol, E. Fischer and Zach[94] prepared 6-bromo-2,3,5-triacetyl-menthyl glucoside, which is probably a β form on account of its origin by Koenigs and Knorr's synthesis. By boiling it with alcoholic sodium hydroxide solution the acetyl groups were removed in the usual way, but the bromine atom formed hydrobromic acid and there resulted an internal anhydride of menthyl glucoside, its carbon 6 being united through an oxygen atom to some other carbon atom of the chain, the identity of which is at present not known. They suggest the rings 6,5 and 6,3 as probabilities. On account of the uncertainty this substance will be here referred to as 6,*x*-anhydro-menthyl glucoside. If the rotation of its basal chain be b_x its molecular rotation (mol. wt., 300; $[\alpha]_D = -96$ in alcohol; hence $[M]_D = -28{,}800$) may be written $b_x - a_{menthyl} - c_{menthyl} = b_x - 25{,}100 - 16{,}600 = -28{,}800$, and hence $b_x = 12{,}900$ in alcohol. Now, from dibromo-acetyl glucose and methyl alcohol E. Fischer and Armstrong[95] have prepared 6-bromo-2,3,5-triacetyl methyl glucoside, doubtless a β compound, and by boiling this with an aqueous-alcoholic solution of barium hydroxide E. Fischer and Zach have made an anhydro methyl glucoside, which will be designated here as 6,y-anhydro-methyl glucoside. The question arises, is y the same as x, that is, does this anhydro-methyl glucoside possess the same anhydro ring as the anhydro-methyl glucoside previously mentioned? If such is the case, it should be possible to calculate the rotation of the anhydro-methyl glucoside from the value of b_x that has just been found from the rotation of the anhydro-menthyl glucoside. If the substance is a β-glycoside, as seems probable, its specific rotation is calculated to be $(b_x - a_{methyl}) \div$ mol. wt. $= (12{,}900 - 18{,}500^{96}) \div 176 = -32$, while if it is an α form $(b_x + a_{methyl}) \div$ mol. wt. $= +178$. Fischer and Zach purified their 6,y-anhydro-methyl glucoside by distillation in a high vacuum and the uncrystallizable sirup showed $[\alpha]_D = -137$. This value is so greatly different from those calculated that it appears probable that the assumption of the identity of x and y is incorrect and that on the contrary the two anhydro-glucosides should be regarded as derivatives of anhydro-glucoses of different structures. Possibly one is a 6,5- and the other a 6,3-anhydro-glucose.

(d) THE CRYSTALLINE LACTONE OF *d*-GLUCURONIC ACID

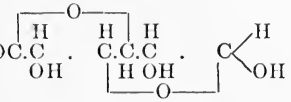
The configuration of this lactone may be regarded as shown in (III) in case the aldehyde formula of glucose is assumed, or as in (IV) if the Tollens formula for glucose is accepted. Attention may be

[93] Hudson, Jour. Am. Chem. Soc., **46**, 462; 1924 (p. 320).
[94] E. Fischer and Zach, Ber., **45**, 456; 1912.
[95] Fischer and Armstrong, Ber., **35**, 833; 1902.
[96] This value of a_{methyl} in water is taken from article 7.

called to the asymmetry of carbon 1 in Structure IV, the possible significance of which seems to have escaped notice in the past. It is obvious that if this structure applies, the occurrence of the lactone in α and β forms similar to those of glucose becomes a possibility.



(III)



(IV)

In like manner it is conceivable that the salts, amides, and many other derivatives of glucuronic acid may occur in similar α and β forms. Such isomers may be found to exhibit mutarotation.

(e) SUMMARY OF RESULTS

It has been shown from the data of the literature that Van 't Hoff's principle of optical superposition applies to the rotations of the menthyl glucosides, maltoside, lactoside, and the menthyl-glucoronic acids and probably also to the bornyl glucosides. The calculations supplement those of article 3 in illustrating how the method of comparing rotations can be applied to glycosides of optically active alcohols. The conclusion that the menthyl-glucuronic acids conform to the principle makes it probable that it applies in general to the numerous conjugated glucuronic acids that have been found to be eliminated in the urine under normal or experimental conditions of feeding. On the basis of rotatory data it seems unlikely that 6,*x*-anhydro-menthyl glucoside and 6,*y*-anhydro-methyl glucoside are derivatives of the same anhydro-glucose. Lastly, it is pointed out on theoretical grounds that glucuronic lactone and the salts, amides, etc., of glucuronic acid may possibly occur in two isomeric forms corresponding to the α and β forms of glucose and may exhibit mutarotation.

9. THE ROTATION OF THE ALPHA FORM OF METHYL GENTIOBIOSIDE RECENTLY SYNTHESIZED BY HELFERICH AND BECKER[97]

In 1917 Hudson and Johnson showed that the rotations of several derivatives of gentiobiose could be calculated, including the α and β forms of methyl gentiobioside, the hepta-acetates of these glycosides, and the α form of gentiobiose octa-acetate. They prepared for the first time three of these five substances and found a good agreement between the calculated and observed rotations, as follows: α-gentiobiose octa-acetate, observed $+52°$ (in chloroform), calculated $+52°$; β-methyl gentiobioside, observed $-36°$ (in water), calculated $-38°$; β-methyl gentiobioside hepta-acetate, observed $-19°$ (in chloroform), calculated $-17°$. The α form of methyl gentiobioside and its hepta-acetate were unknown and were not prepared because of the lack of

[97] C. S. Hudson, Jour. Am. Chem. Soc. 47, 872-873; 1925.

a suitable method of synthesis for this α glycoside, but the rotations of these substances were calculated to be, for α-methyl gentiobioside, +65 in water, and for its hepta-acetate, +66 in chloroform. (See p. 267.)

Helferich and Becker[98] have recently synthesized a substance which they regard as α-methyl gentiobioside. It crystallizes with one molecule of alcohol of crystallization, and they record two measurements of its rotatory power, one referring to the substance after drying over phosphorus pentoxide at the relatively high temperature of 142° ($[\alpha]_D^{2.3} = +61.8$ in water) and the other referring to the substance containing alcohol of crystallization (11.4 per cent of alcohol) ($[\alpha]_D^{2.4} = +59.4$ in water). If the latter measurement be referred to dry material $[\alpha]_D^{2.4} = +67.0$. They mention (loc. cit. p.7) that the limit of error in these determinations is considerable because a sensitive polariscope was not available for their use. The average of their results, $[\alpha]_D = +64$ for α-methyl gentiobioside in aqueous solution, agrees satisfactorily with the rotation that Hudson and Johnson calculated (+65). Doubtless it will be only a matter of time before the rotation of α-methyl gentiobioside hepta-acetate in chloroform solution can likewise be measured.[99]

The α and β forms of methyl gentiobioside constitute the first known pair of methyl glycosides of a disaccharide, and the agreement of their observed rotations with those calculated from the rotations of the α and β forms of methyl glucoside on the assumption of Van 't Hoff's principle of optical superposition is a good indication that the method of comparing structures with rotatory powers that is based upon this principle can be extensively employed in structural studies of the sugars and their derivatives. In the present instance, this method furnishes valuable and independent evidence that the substance which Helferich and Becker have synthesized is what they suppose it to be, namely, α-methyl gentiobioside. This evidence is very welcome in the present instance because it confirms in an independent way the chemical evidence (synthetic method, action of enzymes, etc.) by which Helferich and Becker have determined the constitution of the compound.

10. THE CHLORO-, BROMO-, AND IODO-ACETYL DERIVATIVES OF LACTOSE[1]

When it was shown in article 1 that the rotation of the end asymmetric carbon atom of a halogeno-acetyl aldose is approximately a constant quantity, namely, one of the coefficients A_F, A_{Cl}, A_{Br} or A_I, for nearly all the aldoses, it was stated that the value of A_{Cl}

[98] Helferich and Becker, Ann., **440**, 1; 1924.

[99] Under date of Nov. 14, 1925, Doctor Helferich writes the author that recent careful measurements show for pure α-methyl gentiobioside $[\alpha]_D^{1.9} = +65.5$ in water and for its hepta-acetate +64.5 in chloroform. These values agree closely with the rotations that were calculated in 1917. See Helferich, Klein and Shäfer, Ann., **447**, 26; 1926.

[1] C. S. Hudson and Alfons Kunz, Jour. Am. Chem. Soc., **47**, 2052; 1925.

for chloro-acetyl lactose that was derived from Bodart's record of the specific rotation of this substance in chloroform ($[\alpha]_D = +72$) "is somewhat low and should be reexamined." This revision has now been made and it has been found that Bodart's rotation is much too low, the correct $[\alpha]_D$ being $+84$, in good agreement with the calculated value. The specific rotation of carefully purified bromo-acetyl lactose has likewise been remeasured and found to be 109°, which is somewhat larger than previous determinations (105°) and agrees closely with the calculated value. The rotation of pure iodo-acetyl lactose, which has not previously been recorded, although the compound was prepared in 1912 by W. Sloan Mills, has been found to be $[\alpha]_D = +137$, in good agreement with that calculated. The newly measured rotations of these three halogeno-acetyl lactoses and the resulting values of the A coefficients are recorded in Table 38. The values of A agree closely with those previously obtained from the rotations of the corresponding derivatives of cellobiose and glucose,[2] which proves that the halogeno-acetyl derivatives of lactose follow closely the generalization that was advanced in article 1. The positive values of A for these halogeno-acetyl sugars indicate that the substances are α forms, as was previously mentioned in article 1.

TABLE 38.—*The value of the quantity A, the rotation of the end asymmetric carbon atom, for chloro-, bromo-, and iodo-acetyl lactose*

Lactose	Molecular weight	$[\alpha]_D^{20-5}$ in $CHCl_3$	$[M]_D$	Rotation [1] of end carbon	A for corresponding derivative of—	
					Cellobiose	Glucose
α-Chloro-acetyl	655	+84	+55,000	+38,100(A_{Cl})	+39,000	+40,200
α-Bromo-acetyl	699	+109	+76,200	+59,300(A_{Br})	+58,300	+60,700
α-Iodo-acetyl	746	+137	+102,200	+85,300(A_I)	+85,200	[2] +87,800

[1] $A = [M]_D - 16{,}900$. This number is the value of $B_{lactose}$ from the rotations of the α and β forms of lactose octa-acetate (see article I, p. 311).

[2] This value, which is somewhat larger than that recorded in article 1 (+85,600) is obtained from the $[\alpha]_D$ of iodo-acetyl glucose in chloroform (+237), recently published by D. H Brauns, Jour. Am. Chem. Soc., **47**, 1280; 1925.

It seems very probable that α-fluoro-acetyl lactose, a substance that is now unknown, will be found to have the rotation that can be calculated in the usual manner by aid of the coefficient $A_F = +9{,}800$, which was found in article 1 from the rotations of the fluoro-acetyl derivatives of xylose, glucose and cellobiose that D. H. Brauns has prepared. Thus, $[\alpha]_D = (B_{lactose} + A_F) \div$ mol. wt. $= (16{,}900 + 9{,}800) \div 638 = +42°$ for fluoro-acetyl lactose in chloroform.

The rotations that may be expected for the corresponding β-halogeno-acetyl lactoses can be calculated similarly. Thus, for β-chloro-

[2] C. S. Hudson, Jour. Am. Chem. Soc., **46**, 462; 1924.

acetyl lactose the calculated value is $[\alpha]_D = (B_{lactose} - A_{Cl}) \div$ mol. wt. $= (16{,}900 - 38{,}100) \div 655 = -32°$ in chloroform.

(a) EXPERIMENTAL PART

(1) ACETYLATION OF LACTOSE.—Lactose octa-acetate, the material from which the halogeno-acetyl lactoses were prepared, was made by heating to a temperature near boiling 100 g of commercial milk sugar (α-lactose monohydrate) with 600 cc of acetic anhydride (96 per cent strength) and 300 cc of pure, dry pyridine, during half an hour, pouring the cooled solution into about 5 liters of ice water and washing the precipitated acetate with ice water. The granular, white material was filtered off, washed with ice water, and dried in the air; yield, 168 g, or 89 per cent. The rotation of the substance ($[\alpha]_D = +21$ in $CHCl_3$) indicates that it is a mixture of the α and β lactose octa-acetates, the β form predominating slightly. It may be used without further purification for preparing the halogeno-acetyl lactoses in good yield and will be referred to as crude lactose octa-acetate.

(2) PREPARATION OF α-CHLORO-ACETYL LACTOSE ($C_{12}H_{14}O_{10}(C_2H_3O)_7Cl$).—Twenty g of crude lactose octa-acetate was dissolved in 100 cc of chloroform, 10 g of phosphorus pentachloride and 5 g of anhydrous aluminum chloride were added and the mixture was gently boiled 1.5 hours, after which it was cooled, washed thrice with ice water, dried with calcium chloride, and evaporated under reduced pressure to about 25 cc. After the addition of 300 cc of ether, crystallization of chloro-acetyl lactose took place rapidly; yield, 10 g, or 50 per cent. The colorless needles gave $[\alpha]_D^{23} = +79°$ in chloroform. After four recrystallizations from chloroform and ether, $[\alpha]_D^{25} = +83.8$ (1.0318 g of substance made up to 100 cc of solution in pure chloroform rotated sodium light 5.19 to the right at 25°, the tube length being 6 dcm). After another recrystallization, $[\alpha]_D^{22.5} = +84.0$ (0.9088 g of substance, 100 cc of solution in chloroform, 6 dcm tube; rotation, 4.58 to the right). The average value, $[\alpha]_D^{20-5} = +83.9$, is accepted for the range 20 to 25° in dilute chloroform solution. The substance melts at 120 to 121° to a colorless liquid, which slowly decomposes. It is a very stable halogeno-acetyl sugar, as a sample of the crystals after six weeks' standing in a loosely stoppered bottle was unchanged, showing $[\alpha]_D^{22} = +84.4$ in chloroform (0.4895 g of substance, 50 cc of solution in chloroform, a 6 dcm tube; rotation, 4.96 to the right) and $[\alpha]_D^{23} = +68.2$ in benzene (0.4823 g of substance, 50 cc of solution in benzene, a 6 dcm tube; rotation, 3.95 to the right).

The only previous record of its rotation in chloroform is that of Bodart,[3] who found $[\alpha]_D^{20} = +72$ for a preparation melting at 119 to 121°. In benzene, E. Fischer and E. F. Armstrong[4] found $[\alpha]_D^{20} = +73.5$

[3] Bodart, Monatsh., 23, 5; 1902.

[4] Fischer and Armstrong, Ber., 35, 833; 1902.

for a material melting at 118 to 120° and $[\alpha]_D^{20} = +76$ for one melting at 57 to 59°, which they supposed to be an isomeric form. We have not met this supposed isomer of low melting point and our rotation in benzene for pure chloro-acetyl lactose is considerably different from either of Fischer and Armstrong's values.

On one occasion, upon the addition of petroleum ether to the mother liquor of an original crystallization of α-chloro-acetyl lactose, which had been prepared from 20 g of crude lactose octa-acetate, there slowly separated about 1 g of a crystalline substance in the form of prisms which showed $[\alpha]_D^{25} = +71.7$ in chloroform, melted at 160° and gave a strong chlorine reaction with silver nitrate. It seems to be a new chlorine derivative of lactose octa-acetate and is being examined further.

(3) Preparation of α-Bromo-acetyl Lactose ($C_{12}H_{14}O_{10}(C_2H_3O)_7$ Br).—The substance was prepared from crude lactose octa-acetate and a 40 per cent solution of hydrogen bromide in glacial acetic acid according to E. Fischer and H. Fischer's directions,[5] except that the temperature was kept low by an ice-bath in an effort to increase the yield. However, the same yield that they found was obtained, 80 to 85 per cent. Two crystallizations from chloroform by the addition of ether were sufficient for purification to constant rotation, which was $[\alpha]_D^{23} = +108.7$ (1.0118 g of substance made up to 100 cc of solution in pure chloroform rotated sodium light in a 6 dcm tube 6.60° to the right at 23°). It melted at 145° with decomposition. E. Fischer and H. Fischer record $[\alpha]_D^{22} = +104.9$ in chloroform; m. p., 141 to 142°. Ditmar [6] records $[\alpha]_D^{14} = +108.17$ in chloroform; m. p., 138°.

(4) Preparation of α-Iodo-acetyl Lactose ($C_{12}H_{14}O_{10}(C_2H_3O)_7$ I).—Ten g of crude lactose octa-acetate was dissolved in 50 cc of a 20 per cent solution of hydrogen iodide in glacial acetic acid and the solution was kept at room temperature (20 to 25°) for 45 minutes. On pouring the solution into ice water a yellow precipitate separated. It was filtered off, dissolved in chloroform and the solution washed with dilute sodium thiosulphate solution, which decolorized it, and then washed again with ice-water. It was dried with calcium chloride and evaporated under reduced pressure to about 10 cc. On the addition of ether, crystallization took place immediately; yield, 6.5 g, or 59 per cent. Recrystallization from chloroform by the addition of ether did not change the rotation, which was $[\alpha]_D^{23} = +136.9°$ (0.9475 g of substance made up to 100 cc of solution in pure chloroform rotated sodium light in a 6 dcm tube 7.78 to the right at 23°). The iodine percentage was found to be 17.3 in comparison with 17.01 calculated for iodo-acetyl lactose (0.1730 g of substance yielded

[5] E. Fischer and H. Fischer, Ber., **43**, 2521; 1910. [6] Ditmar, Monatsh., **23**, 865; 1902.

0.0516 g of silver iodide). The melting point was 145° with decomposition. W. Sloan Mills,[7] who first prepared iodo-acetyl lactose, found a melting point of 142°, but did not record a rotation.

One of the authors (A. K.) expresses his thanks to the International Education Board for a grant which enabled him to take part in this research.

(b) SUMMARY

The specific rotation of pure iodo-acetyl lactose has been measured, and the specific rotations of chloro- and of bromo-acetyl lactose have been remeasured; all have been found to agree with the theoretical requirements.

IV. TABLE OF ROTATIONS OF PURE SUBSTANCES WHICH HAVE BEEN MEASURED IN THE COURSE OF THESE RESEARCHES

Substance [1]	Formula	Molecular weight	M. P.	$[\alpha]_D$	$[M]_D$	Solvent
			C°			
β-*d*-Arabinose	$C_5H_{10}O_5$	150		−175.0	−26,300	H_2O.
α-*l*-Arabinose tetra-acetate [2]	$C_{13}H_{18}O_9$	318	97	+42.5	+13,500	$CHCl_3$.
β-*l*-Arabinose tetra-acetate [3]	$C_{13}H_{18}O_9$	318	86	+147.2	+46,800	$CHCl_3$.
l-Arabonic amide	$C_5H_{11}O_5N$	165	136	+37.5	+6,190	H_2O.
d-Arabonic phenylhydrazide	$C_{11}H_{16}O_5N_2$	256		−14.5	−3,710	H_2O.
β-Bromo-acetyl *d*-arabinose	$C_{11}H_{15}O_7Br$	339		−288.0	−97,600	$CHCl_3$.
β-Bromo-acetyl *l*-arabinose	$C_{11}H_{15}O_7Br$	339		+288.0	+97,600	$CHCl_3$.
α-Bromo-acetyl lactose	$C_{26}H_{35}O_{17}Br$	699	145	+109.0	+76,200	$CHCl_3$.
α Bromo-acetyl *d*-xylose	$C_{11}H_{15}O_7Br$	339	102	+212.0	+71,900	$CHCl_3$.
β-Cellobiose	$C_{12}H_{22}O_{11}$	342		+16.0	+5,470	H_2O.
α-Cellobiose octa-acetate	$C_{28}H_{38}O_{19}$	678	229	+41.0	+27,800	$CHCl_3$.
β-Cellobiose octa-acetate	$C_{28}H_{38}O_{19}$	678	202	−14.6	−9,900	$CHCl_3$.
α-Chondrosamine penta-acetate	$C_{16}H_{23}O_{10}N$	389	183	+101.3	+39,400	$CHCl_3$.
β-Chondrosamine penta-acetate	$C_{16}H_{23}O_{10}N$	389	220	+10.5	+4,080	$CHCl_3$.
β-Chloro-acetyl *d*-arabinose	$C_{11}H_{15}O_7Cl$	295		−244.0	−72,000	$CHCl_3$.
β-Chloro-acetyl *l*-arabinose	$C_{11}H_{15}O_7Cl$	295		+244.0	+72,000	$CHCl_3$.
Chloro-acetyl *d*-galactose (second)	$C_{14}H_{19}O_9Cl$	367	67	−78.0	−28,600	$CHCl_3$.
α-Chloro-acetyl lactose	$C_{26}H_{25}O_{17}Cl$	655	121	+84.0	+55,000	$CHCl_3$.
β-*d*-Fructose	$C_6H_{12}O_6$	180		−133.5	−24,000	H_2O.
α-*d*-Fructose penta-acetate	$C_{16}H_{22}O_{11}$	390	70	+34.7	+13,500	$CHCl_3$.
β-*d*-Fructose penta-acetate	$C_{16}H_{22}O_{11}$	390		−120.9	−47,200	$CHCl_3$.
β-*d*-Fructose tetra-acetate	$C_{14}H_{20}O_{10}$	348		−91.6	−31,900	$CHCl_3$.
d-Galactonic amide	$C_6H_{13}O_6N$	195	172	+30.2	+5,890	H_2O.
α-*d*-Galactose	$C_6H_{12}O_6$	180		+144.0	+25,900	H_2O.
β-*d*-Galactose	$C_6H_{12}O_6$	180		+52.0	+9,360	H_2O.
d-Galactose penta-acetate (first)	$C_{16}H_{22}O_{11}$	390	142	+23.0	+8,970	$CHCl_3$.
d-Galactose penta-acetate (second)	$C_{16}H_{22}O_{11}$	390	96	+107.0	+41,700	$CHCl_3$.
d-Galactose penta-acetate (third)	$C_{16}H_{22}O_{11}$	390	98	−42.0	−16,400	$CHCl_3$.
d-Galactose penta-acetate (fourth)	$C_{16}H_{22}O_{11}$	390	87	+61.0	+23,800	$CHCl_3$.
d-Galactose tetra-acetate (third)	$C_{14}H_{20}O_{10}$	348	73	−17.8	−6,190	$CHCl_3$.
Phenylhydrazone of the above subs	$C_{20}H_{26}O_9N_2$	438	95	+15.5	+6,790	$CHCl_3$.
d-α-Galaheptonic amide	$C_7H_{15}O_7N$	225	206	+14.3	+3,220	H_2O.
d-α-Galaheptonic phenylhydrazide [4]	$C_{13}H_{20}O_7N$	316		+8.5	+2,700	H^2O.
α-Gentiobiose octa-acetate	$C_{28}H_{38}O_{19}$	678	189	+52.4	+35,500	$CHCl_3$.
β-Gentiobiose octa-acetate	$C_{28}H_{38}O_{19}$	678	193	−5.3	−3,590	$CHCl_3$.
d-α-Glucoheptonic amide	$C_7H_{15}O_7N$	225	134	+10.6	+2,390	H_2O.
d-β-Glucoheptonic amide	$C_7H_{15}O_7N$	225	158	−30.2	−6,790	H_2O.
d-α-Glucoheptonic phenylhydrazide	$C_{13}H_{20}O_7N_2$	316		+9.3	+2,940	H_2O.
β-*d*-α-Glucoheptose	$C_7H_{14}O_7$	210		−28.4	−5,960	H_2O.
α-*d*-α-Glucoheptose hexa-acetate	$C_{19}H_{26}O_{13}$	462	164	+87.0	+40,200	$CHCl_3$.

[1] Measured at 20°, except as indicated in footnotes [2], [3], [4], and [5].
[2] Measured at 22°.
[3] Measured at 21°.
[4] Measured at 80°.

[7] W. Sloan Mills, Chem. News, **106**, 165; 1912.

IV. TABLE OF ROTATIONS OF PURE SUBSTANCES WHICH HAVE BEEN MEASURED IN THE COURSE OF THESE RESEARCHES—Continued

Substance	Formula	Molecular weight	M. P.	$[\alpha]_D$	$[M]_D$	Solvent
			C°			
β-*d*-α-Glucoheptose hexa-acetate	$C_{19}H_{26}O_{13}$	462	135	+4.8	+2,220	$CHCl_3$.
d-Gluconic amide	$C_6H_{13}O_6N$	195	144	+31.2	+6,080	H_2O.
α-*d*-Glucosamine penta-acetate	$C_{16}H_{23}O_{10}N$	389	140	+93.5	+36,400	$CHCl_3$.
β-*d*-Glucosamine penta-acetate	$C_{16}H_{23}O_{10}N$	389	189	+1.2	+467	$CHCl_3$.
α-*d*-Glucose	$C_6H_{12}O_6$	180	------	+113.0	+20,300	H_2O.
β-*d*-Glucose	$C_6H_{12}O_6$	180	------	+19.0	+3,420	H_2O.
α-*d*-Glucose penta-acetate	$C_{16}H_{22}O_{11}$	390	113	+101.6	+39,600	$CHCl_3$.
β-*d*-Glucose penta-acetate	$C_{16}H_{22}O_{11}$	390	132	+3.8	+1,480	$CHCl_3$.
d-Gulonic amide	$C_6H_{13}O_6N$	195	123	+15.2	+2,960	H_2O.
α-Iodo-acetyl lactose	$C_{26}H_{35}O_{17}I$	746	145	+137.0	+102,000	$CHCl_3$.
α-Lactose	$C_{12}H_{22}O_{11}$	342	------	+90.0	+30,800	H_2O.
β-Lactose	$C_{12}H_{22}O_{11}$	342	------	+35.0	+12,000	H_2O.
α-Lactose octa-acetate	$C_{28}H_{38}O_{19}$	678	152	+53.9	+36,500	$CHCl_3$.
β-Lactose octa-acetate	$C_{28}H_{38}O_{19}$	678	90	−4.3	−2,920	$CHCl_3$.
α-*d*-Lyxose	$C_5H_{10}O_5$	150	------	+5.5	+825	H_2O.
β-Maltose	$C_{12}H_{22}O_{11}$	342	------	+118.0	+40,400	H_2O.
β-Maltose hepta-acetate	$C_{26}H_{36}O_{18}$	636	181	+67.8	+43,100	$CHCl_3$.
α-Maltose octa-acetate	$C_{28}H_{38}O_{19}$	678	125	+122.4	+83,000	$CHCl_3$.
β-Maltose octa-acetate	$C_{28}H_{38}O_{19}$	678	160	+62.7	+42,500	$CHCl_3$.
d-Mannitol hexa-acetate	$C_{18}H_{26}O_{12}$	434	120	+26.0	+11,300	$CHCl_3$.
d-α-Mannoheptonic amide	$C_7H_{15}O_7N$	225	194	+28.0	+6,300	H_2O.
d-α-Mannoheptonic phenylhydrazide [4]	$C_{13}H_{20}O_7N_2$	316	------	+21.0	+6,640	H_2O.
d-α-Mannoheptose hexa-acetate (first)	$C_{19}H_{26}O_{13}$	462	106	+24.2	+11,200	$CHCl_3$.
d-α-Mannoheptose hexa-acetate (second)	$C_{19}H_{26}O_{13}$	462	140	−31.0	−14,300	$CHCl_3$.
d-Mannonic amide	$C_6H_{13}O_6N$	195	173	−17.3	−3,370	H_2O.
d-Mannonic phenylhydrazide [4]	$C_{12}H_{18}O_6N_2$	286	------	−8.1	−2,320	H_2O.
d-Mannosaccharic di-amide	$C_6H_{12}O_6N_2$	208	189	−24.5	−5,100	H_2O.
β-*d*-Mannose	$C_6H_{12}O_6$	180	------	−17.0	−3,060	H_2O.
α-*d*-Mannose penta-acetate	$C_{16}H_{22}O_{11}$	390	64	+55.0	+21,500	$CHCl_3$.
β-*d*-Mannose penta-acetate	$C_{16}H_{22}O_{11}$	390	118	−25.2	−9,830	$CHCl_3$.
Melezitose	$C_{18}H_{32}O_{16}$	504	148	+88.2	+44,500	H_2O.
Melezitose hendeka-acetate	$C_{40}H_{54}O_{27}$	966	117	+103.8	+100,000	$CHCl_3$.
β-Melibiose	$C_{12}H_{22}O_{11}$	342	------	+124.0	+42,400	H_2O.
β-Melibiose octa-acetate	$C_{28}H_{38}O_{19}$	678	177	+102.5	+69,500	$CHCl_3$.
α-Methyl *l*-arabinoside	$C_6H_{12}O_5$	164	131	+17.3	+2,840	H_2O.
β-Methyl *l*-arabinoside	$C_6H_{12}O_5$	164	169	+245.5	+40,300	H_2O.
β-Methyl *l*-arabinoside tri-acetate [5]	$C_{12}H_{18}O_8$	290	85	+182.0	+52,800	$CHCl_3$.
β-Methyl cellobioside hepta-acetate	$C_{27}H_{38}O_{18}$	650	187	−25.4	−16,500	$CHCl_3$.
β-Methyl *d*-fructoside	$C_7H_{14}O_6$	194	120	−172.1	−33,400	H_2O.
β-Methyl *d*-fructoside tetra-acetate	$C_{15}H_{22}O_{10}$	362	76	−124.6	−45,100	$CHCl_3$.
α-Methyl *d*-galactoside tetra-acetate	$C_{15}H_{22}O_{10}$	362	------	+133.0	+48,100	$CHCl_3$.
β-Methyl *d*-galactoside tetra-acetate	$C_{15}H_{22}O_{10}$	362	------	−13.0	−4,710	$CHCl_3$.
β-Methyl gentiobioside	$C_{13}H_{24}O_{11}$	356	98	−36.0	−12,800	H_2O.
β-Methyl gentiobioside hepta-acetate	$C_{27}H_{38}O_{18}$	650	82	−18.9	−12,300	$CHCl_3$.
α-Methyl *d*-glucoside tetra-acetate	$C_{15}H_{22}O_{10}$	362	101	+130.6	+47,300	$CHCl_3$.
β-Methyl *d*-glucoside tetra-acetate	$C_{15}H_{22}O_{10}$	362	105	−18.3	−6,620	$CHCl_3$.
β-Methyl maltoside hepta-acetate	$C_{27}H_{38}O_{18}$	650	125	+53.7	+34,900	$CHCl_3$.
α-Methyl *d*-xyloside	$C_6H_{12}O_5$	164	------	+153.9	+25,200	H_2O.
β-Methyl *d*-xyloside	$C_6H_{12}O_5$	164	157	−65.5	−10,700	H_2O.
α-Methyl *d*-xyloside tri-acetate	$C_{12}H_{18}O_8$	290	86	+119.6	+34,700	$CHCl_3$.
β-Methyl *d*-xyloside tri-acetate	$C_{12}H_{18}O_8$	290	115	−60.7	−17,600	$CHCl_3$.
l-Rhamno-methyl-tetronic amide	$C_5H_{11}O_4N$	149	135	+54.8	+8,170	H_2O.
l-Rhamno-methyl-tetronic lactone	$C_5H_8O_4$	132	123	−44.7	−5,900	H_2O.
l-Rhamnonic phenylhydrazide [4]	$C_{12}H_{18}O_5N_2$	270	------	+17.2	+4,640	H_2O.
α-*l*-Rhamnose	$C_6H_{12}O_5$	164	------	−7.7	−1,260	H_2O.
l-Ribonic amide	$C_5H_{11}O_5N$	165	138	−16.4	−2,710	H_2O.
d-Saccharic di-amide	$C_6H_{12}O_6N_2$	208	173	+13.3	+2,770	H_2O.
Sedoheptose (anhydro-)	$C_7H_{12}O_6$	192	------	−146.3	−30,720	H_2O.
Sucrose octa-acetate	$C_{28}H_{38}O_{19}$	678	69	+59.6	+40,400	$CHCl_3$.
Trehalose octa-acetate	$C_{28}H_{38}O_{19}$	678	98	+162.3	+110,000	$CHCl_3$.
α-*d*-Xylose	$C_5H_{10}O_5$	150	------	+92.0	+13,800	H_2O.
α-*d*-Xylose tetra-acetate	$C_{13}H_{18}O_9$	318	59	+89.1	+28,300	$CHCl_3$.
β-*d*-Xylose tetra-acetate	$C_{13}H_{18}O_9$	318	128	−24.9	−7,920	$CHCl_3$.
d-Xylose tri-acetate [5]	$C_{11}H_{16}O_8$	276	141	+70.0	+19,300	$CHCl_3$.

[4] Measured at 80°.

[5] Measured at 23°.

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